THE CLINICAL EPIDEMIOLOGY AND TREATMENT OF NEUROMYELITIS OPTICA

Thesis submitted in accordance with the requirements of the University of Liverpool for the degree of Doctor in Medicine

by

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Contents

PREFACE

Neuromyelitis optica has been traditionally considered an inflammatory demyelinating disease of the nervous system similar to multiple sclerosis but with a poorer outcome. Early descriptions were made by Albutt in 1870. Subsequently Eugene Devic (1894) summarised the known cases and literature and the disease carries his name. There had been sporadic case reports throughout literature in the last century and small case series. In 1999 the Mayo Clinic reported a large series and suggested diagnostic criteria. Only a case series has been published from the United Kingdom. This study intended to identify patients across the United Kingdom, and prospectively follow them up characterising clinical epidemiological features, treatments and long-term outcomes.

Treatments in NMO are anecdotal. I also studied the effects of two treatments – rituximab and mycophenolate in NMO during my fellowship at the Mayo Clinic, USA. However, great advances have been made in NMO in the last five years. A specific autoantibody -NMO IgG was identified by Vanda Lennon and colleagues at the Mayo Clinic. Subsequently the antigen to this antibody was found to be a component of the water channel on the surface of astrocytes, aquaporin-4. More recently glutamate mediated damage has been identified to be a key mechanism of injury. Much has been learned about the pathogenesis and the pathology of NMO. However the epidemiology, long term outcomes and effective treatments are still unclear. I hope this work will might shed some light on these aspects.

ACKNOWLEDGEMENTS

Neuromyelitis optica (NMO) has been the dominant player in my life for the last six years. I had stepped into this unwittingly as a research fellow aiming for higher specialist training in Neurology. Little did I know that I would still be deeply involved in its study for years to come! I must thank Professor David Chadwick who suggested my name to Dr Mike Boggild who was planning a UK wide NMO study. Dr Boggild has been a constant source of support and guidance allowing a free rein. The late Ian Hart who was my supervisor was a great source of wisdom. His achievements in immunology particularly neuromytonia has been inspirational – my only regret is that I could not learn more from him. Professor Solomon has had a long-term interest in NMO and has re-entered the fray as my supervisor to help me complete this work. I have contacted and have been contacted by several Clinicians across the UK and abroad regarding their patients with NMO. Their experiences have helped guide this study. The one-year fellowship with Professor Weinshenker has been a major turning point in my understanding of this disease. I am particularly grateful to Professor Weinshenker, Doctors Sean Pittock, Matiello Marcelo and Bruce Cree for permitting me to utilise the Mayo clinic NMO database and for allowing me to include the rituximab and mycophenolate studies done under their guidance. I have immense gratitude to colleagues at Oxford, (particularly Professor Angela Vincent) Manchester , Mayo clinic and Newcastle who have assisted with the immunologic and genetic essays. I am most grateful to Consultant Neurologists across the UK who has taken the time to refer patients to this study. This would not have been possible without the British Neurological Surveillance Unit and Karen Reeves. Thanks are due to Maria Pybis, Michelle Dennis and Tony Murphy for their contributions. I am indebted to my family who have suffered (not in silence though!) my absences and late nights! More than one hundred patients and their families have been contacted multiple times. They have contributed time, effort, money and blood! I am

hopeful that the results of this study will be beneficial to them and their future management. However there are a few who are now deceased and will not benefit from their contributions. It is to these selfless people that I dedicate this work.

DECLARATION

I declare that all the work described in this thesis is my own, with the exceptions mentioned in the acknowledgements.

Abstract

Clinical Epidemiology and Treatment of Neuromyelitis optica

Anu Jacob

Introduction: Neuromyelitis optica (NMO) is an idiopathic inflammatory demyelinating condition of the central nervous system, which was once considered a variant of multiple sclerosis (MS), restricted to the optic nerve and spinal cord. We now know it to be disease in its own right with striking similarities to MS. There have been remarkable advances in the understanding of its aetiopathogenesis in the last few years. However its epidemiology and effective treatments are still uncertain.

Aims:

Identify, characterise and follow up a cohort of NMO patients from the United Kingdom.
Describe the epidemiology of NMO in Merseyside
Identify new treatments for NMO

Methods: Using the British neurological surveillance unit and the electronic records system of the Walton Centre for Neurology and Neurosurgery, I identified 42 patients with NMO over a 5 year period; I documented their history and examination findings, tested for aquaporin -4 antibodies, oligoclonal bands and autoimmune markers. Using the electronic records system of the Walton Centre for Neurology and Neurosurgery, I indentified all patients with NMO in Merseyside, and described the epidemiology. Finally I examined the role of novel immunomodulatory agents - rituximab (antiCD-20 monoclonal antibody) and mycophenolate in NMO.

Results: 128 patients were seen and 75 patients are still being followed up-a median (range) of 34 months (0.4-71). Forty-two of these patients satisfy current criteria for NMO or NMO spectrum disorders (NMOSD). 81% were positive for the aquaporin-4 antibody. Ten (24%) patients died and all patients had some disability at their last follow up.

In the Merseyside region the prevalence of NMO, NMOSD and the combined group was estimated to be 4.37, 3.49 and 7.86 per million. The incidence was estimated to be 0.52, 0.7 and 1.22 per million per year respectively. These data suggest that there are at least 369 patients with NMO or NMOSD and 57 new patients/year in the United Kingdom. Rituximab was found to reduce relapse rates and stabilise or improve disability in a cohort 25 patients. Mycophenolate was found to reduce relapse rates and stabilise disability in a cohort of 24 patients

Conclusions: The largest prospective study to date again show that NMO and NMO spectrum disorder are disabling conditions with a high mortality and morbidity and aquaporin-4 antibody positivity is common. NMO is commoner than previously thought among the Caucasian population. Two of the largest retrospective analyses of treatment efficacy in NMO have shown the benefit of both rituximab and mycophenolate in reducing relapse rates and preventing the progression of disability.

List of Abbreviations

AAB	Auto antibodies
AQP4	Aquaporin 4
ARR	Annualised relapse rates
AZT	Azathioprine
DMT	Disease modifying treatment
EDSS	Expanded disability status scale
FDA	Food and Drugs Agency
LETM	Longitudinally extensive transverse myelitis
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
NMO	Neuromyelitis optica
NMOSD	Neuromyelitis optica spectrum disorder
NMO IgG	Neuromyelitis optica immunoglobulin G
NNOSD	Non-NMO optico spinal demyelination
OCB	Oligoclonal bands
ON	Optic neuritis
OSD	Opticospinal demyelination
OSMS	Opticospinal multiple sclerosis
BNSU	British Neurological Surveillance unit
TM	Transverse myelitis
WCNN	Walton Centre for Neurology and Neurosurgery
OSD-U	Optico spinal demyelination - Unclassified

Chapter 1.

Introduction and review of literature

Introduction 1.1.

Neuromyelitis Optica (NMO) or Devic's disease was first described by Allbutt, who in 1870 reported a patient with a "sympathetic disorder of the eye" after an acute episode of myelitis.(1) A quarter of a century later Eugene Devic and his student Gault 16 cases from the literature in addition to one of their own and the syndrome came to be known as Devic's disease (2)

Our understanding of NMO did not change greatly over the course next century. It remained largely regarded as an unusual or severe variant of Multiple Sclerosis. However the last decade has seen major advances in our understanding of the etiopathogenesis of NMO.

There are now firm reasons to believe that NMO is a distinct immune mediated, largely relapsing, inflammatory, demyelinating disease of the central nervous system (CNS). It most commonly targets the optic nerves and spinal cord, with longitudinally extensive spinal cord lesions on MRI being recognized as a characteristic and important diagnostic finding. We also now recognize that brain lesions can occur in NMO, though are usually atypical for MS. We also know that a specific serum antibody (NMO-IgG) which reacts specifically with aquaporin 4 (AQP4) is present in up to 70% of patients (3) NMO is the first and the only CNS inflammatory demyelinating disorder to date in which a specific immunologic marker and its target have been identified.

1.2 Epidemiology and Genetics

The exact incidence and prevalence data are hard to obtain in western populations as a result of the rarity of disease in Caucasian populations. In Japan, 15-40% of cases of

demyelinating disease are "optico-spinal" (Kira, 2003). But whether these are truly NMO or a mix of western type MS, with predominant optic and spinal involvement, and true NMO is uncertain. In NMO cohorts from Northern Europe and North America non-Caucasians (African, Hispanic and Asian) are over-represented, though Caucasians still comprise the majority of patients in these series. It has been estimated that NMO represents no more than 1% of patients with demyelinating disease in Western populations.

A recent survey from 2003-2004 covered the Cuban white and non-white population. Prevalence was 5.1 per 1000,000 for the total Cuban population(4).The estimated average annual incidence rate was 0.53 per 1000,000. Neither of these rates differed significantly among whites, blacks, mixed, or non-whites. The number of cases however is far too small to assert the presence or absence of any racial/ethnic predilection for NMO. The prevalence rates by gender demonstrated a much higher rate in females (9.1) than in males (1.2). Regardless of geographic variability NMO may still be an under diagnosed condition, often mislabelled as MS. It is to be hoped that with increasing awareness and availability of MRI and NMO-IgG testing a clearer picture will emerge.

A small number of cases of familial NMO have been reported. The first such case involving identical twin sisters, one who developed the illness at age 24 and the other at age 26(5) two sisters with bilateral ON followed by myelitis at 2 and 3 year(6); two Japanese sisters aged 62 and 67 and two sisters of Spanish-American ancestry, who developed NMO at ages 26 and 28 (7, 8)

Amongst Japanese patients HLA *DRB1*1501*, the allele that is most strongly associated with MS in western countries, is not associated with OSMS, although it is associated with Japanese "classical" MS(9). HLA *DP*0501* has been reported to be over-represented in

Japanese patients with OSMS but this allele has a high frequency in the general Japanese population thus complicating the analysis of such an association(10).

1.3 Clinical Features

NMO is largely relapsing (> 80%) though a minority may have only a monophasic course. Relapsing NMO in the west has a female to male ratio of 5:1. Monophasic NMO affects both sexes equally. The median age of onset in Caucasians is in the fourth decade. (11)Paediatric cases have been reported (12, 13)

NMO is characterised by ON and transverse myelitis. The ON can be unilateral or bilateral, simultaneous or separated by years. It is typically more severe than an ON attack caused by MS. The myelitis too is usually severe and typically causes substantial disability at its nadir. Imaging done acutely almost always shows a longitudinally extensive myelitis (LETM), often with cord oedema and gadolinium enhancement.

Brain stem involvement can occur, usually as an extension of a severe cervical myelitis, and may cause hiccoughs, intractable nausea or respiratory failure (14)

Clinical brain involvement is uncommon but has been reported particularly in pediatric populations. Paroxysmal tonic spasms, which are sequelae of the myelitis, are more common in NMO compared with prototypic MS. Typically these last 10–30 seconds and are characterized by painful contractions of a limb musculature (they can be mistaken for partial seizures or may be labelled functional). It is important to recognize these as they readily respond to small doses of carbamazepine.

NMO coexists with other auto-immune diseases: thyroid, systemic lupus erythematosus (SLE), Sjögren's syndrome (SS), Myasthenia gravis and coeliac disease have all been reported in association with NMO(15). Non-organ specific antibodies, such as antinuclear

antibodies or SSA are found commonly(16). It is important that neurologists recognize that the presence of these alone in the absence of clinical symptoms and signs of their associated systemic disorders should not lead to a diagnosis of a connective tissue disorder as the cause of the myelitis or optic neuritis. It is far more likely that they have NMO with co-existing antibodies reflecting disordered humoral immunity(15). Many of these patients are seropositive for NMO-IgG.

1.3.2 Neuromyelitis optica in Children

NMO in children is similar to those adults. The frequency of NMO-IgG in both childhood and adult cases of NMO, and its rarity in paediatric relapsing-remitting multiple sclerosis, supports the concept that these diseases have a similar pathogenesis in childhood and adulthood. Isolated LETM does not appear to be as predictive of an NMO spectrum disorder in children as it is in adults.

Treating children with immunosuppressants, steroids or monoclonal antibodies is a thorny issue without real consensus. (13)

1.4 Diagnostic Criteria

Several diagnostic criteria have been proposed; the most widely accepted are those put forward by the Mayo group in 1999, which have recently been revised to reflect the importance of spinal cord MRI findings in this disorder (11). With the availability of antibody testing isolated or recurrent episodes of optic neuritis or transverse myelitis (but not both) associated with the antibody have been brought under the category of diseases related to NMO. These (i.e. ON or TM) have been named NMO spectrum disorders (NMOSD). They tend to behave like NMO and should be treated as such (Table1.1)

NMO

Optic neuritis

Acute myelitis

And at least two of three supportive criteria

1. Contiguous spinal cord MRI lesion extending over 3 vertebral segments

2. Brain MRI not meeting diagnostic criteria for multiple sclerosis

3. NMO-IgG seropositive status

NMOSD

Optic neuritis *or* Longitudinally extensive myelitis

And

Presence of NMO IgG or Antiaquaporin-4 antibody

Table 1.1Proposed diagnostic criteria for NMO and NMO SD

1.5 Neuroimaging

Spinal cord MRI undertaken shortly after onset of a sub-acute myelitis (within days to weeks), typically shows a central cord lesion extending over three or more vertebral segments. Longitudinally extensive transverse myelitis (LETM) (Figure 1) with cord oedema and gadolinium enhancement is typical. Follow-up MRI studies may show cord atrophy, syrinx or complete resolution.

Though at disease onset MRI of the brain is usually normal, over time up to 60% will develop non-specific findings. In (10%) they fulfill Barkhof criteria for MS (17). These lesions are largely asymptomatic. Brain stem lesions especially periventricular and hypothalamic lesions have been noted. These are regions of high AQP4 expression, the

target antigen for NMO-IgG (18, 19). Transient encephalopathy or endocrinopathies have been associated with such findings.

Diffusion tensor imaging of normal-appearing brain tissue using has shown abnormal diffusion in patients with NMO, probably related to secondary degeneration caused by lesions in the spinal cord and optic nerve (19)Optic nerve imaging typically shows oedema and contrast enhancement acutely – which may extend from orbit to chiasm - and atrophy at later stages.

1.6 Cerebrospinal fluid

During an acute relapse CSF usually shows a raised total protein with pleocytosis, on occasion 50-500 cells, often neutrophilic and at times leading to diagnostic confusion. Eosinophils may also be found in the CSF in NMO(20). Several inflammatory chemo-attractant cytokines (interleukin [IL]-17 and IL-8, CSF Eotaxin-2, Eotaxin-3 and eosinophil cationic protein) have been found elevated in the CSF of NMO/OSMS patients(21). CSF oligoclonal bands are uncommon, present in only 10-20% patients, representing another differentiating feature from MS. There are several clinical and investigational features, which help to distinguish NMO from MS, these are outlined in table 1.2.

Feature	Multiple Sclerosis	Neuromyelitis optica
Part of nervous system affected	Brain and spinal cord	Usually optic nerves and spinal cord
Non white ancestry	Uncommon	Common
Course	Can be relapsing or progressive	Monophasic or relapsing (progression rare)
Disability	Occurs usually in progressive stage	Occurs earlier (often even after the fi rst event) with severe relapses
MRI	Lesions in brain and small lesions(<2 segments) in spinal cord	Brain lesions not typical for MS. Long lesions in spinal cord with cord swelling (>3 segments)
Spinal fluid oligoclonal bands	Present in >90%	Present in <20%
NMO IgG in serum	Absent	Present in >70%
Systemic autoantibodies	Infrequent	Frequent and multiple
Treatment	Interferons, glatiramer acetate, natalizumab	Immunosuppressants e.g.: Azathioprine, steroids

Table 1.2: Differences between neuromyelitis optica and typical 'Western' MS
Feature MS Neuromyelitis optica

1.7 Pathology

NMO pathology is characterized by presence of inflammation demyelination and necrosis that involves both grey and white matter, often resulting in cavitation. There is presence of vascular hyalinization and eosinophils may be abundant. Perivascular immune complex deposition in a 'rim and rosette' pattern is seen in the spinal cord, brain and optic nerves. More recently, widespread absence of stainable AQP4 in NMO lesions has been demonstrated by several groups (22-24). In some of the lesions described only AQP4 loss

(associated with vasculocentric IgG and IgM deposits and complement activation) without evidence of demyelination or necrosis is seen. This suggests that aquaporin loss could be the earliest pathogenic event in NMO and supports the contention that NMO-IgG plays a central role in the etiopathogenesis of the disorder (22).

1.8 Immunology

In 2004 Lennon et al reported the discovery of NMO-IgG, the first 'disease specific' antibody in CNS demyelinating disease (3). The antibody, identified by immuno-fluorescence has a sensitivity of 73% and specificity 91% for NMO. The antibody is also positive in a significant proportion of patients deemed to be at high risk of NMO-spectrum disorders (that is, patients with isolated or recurrent optic neuritis or myelitis)(3). The specificity of NMO-IgG also called anti AQP4 antibody (in Europe and Japan) has now been independently validated by several groups (25-28). Immunoprecipitation and cell based assays have been developed (25). Of the three methods used in the detection of the antibody, indirect immunofluroscence (NMO IgG), cell based assays and immuno-precipitation (aquaporin 4 antibody) the cell based assays have the highest sensitivity in (90%)(29). Whether NMO-IgG titre correlates with disease severity, attack severity or response to therapy is as yet unknown. No clinical differences between NMO-IgG positive and negative patients meeting current criteria for NMO have been reported in series to date.

1.9 The widening spectrum of NMO

With the availability of NMO-IgG several 'idiopathic/orphan' demyelinating entities can be brought under the NMO 'umbrella'. These include recurrent myelitis without evidence of ON and recurrent ON without evidence of myelitis. In 29 consecutive patients evaluated at Mayo Clinic with a single event of longitudinally extensive transverse myelitis,

40% were seropositive for NMO-IgG (30). Of nine seropositive cases followed for 1 year or longer, 55% (5 patients) had a relapse of myelitis (4 patients) or developed ON (1 patient) within the first year of follow-up; an additional seropositive patient developed ON in the second year of follow-up. In contrast, no seronegative patient had a further neurological event. This finding raises the question of prophylactic or preventative treatment, with the group at Mayo arguing for initiation of immunosuppressive treatment in those patients with an index event (ON or TM) and positive NMO-IgG.

There is increasing evidence that NMO co-exists with a number of systemic connective tissue disorders, particularly SLE and Sjogrens syndrome (SS)(31). Myelitis and optic neuritis hitherto attributed to vasculitic complications of these disorders are most likely due to co-existing NMO (16). In fact approximately half of such patients are seropositive for NMO-IgG, whereas patients with SLE or SS who do not have optic neuritis or myelitis are uniformly seronegative (16)

1.10 Aquaporin 4

The target antigen of NMO-IgG has been recently identified as the water channel protein, aquaporin-4 (AQP4). AQP4 is the dominant water channel within the central nervous system(32). It is located within the CNS on the abluminal wall of small vessels in astrocytic foot processes in close association with the cytoskeleton complex, which includes α-syntrophin, β-dystroglycan, and dystrophin (Dp71). CNS Aquaporin's also play a role in osmoreception, K+ siphoning and CSF formation and are strongly implicated in the pathogenesis of cerebral edema following water intoxication or focal cerebral ischemia(33). Lennon et al have shown that NMO-IgG selectively bind AQP4. Precisely how the AQP4 specific antibodies (NMO-IgG) cause NMO remains uncertain. The antibodies may bind to AQP4 and activate complement initiating a cascade of

inflammation. Alternatively, they may have a functional effect on the water channel, leading to disruption of water homeostasis. More recently glutamate mediated excitotoxicity seems to be player (34). The gene for AQP4 is located on 18q11.2-q12.1. Though no pathogenic mutations have been identified so far, it is conceivable that at least in families with NMO that such a mutation may be involved in its pathogenesis.

1.11 Animal models of NMO

Developing animal models that mirror human disease would be a major step forward in understanding NMO pathogenesis. Development of such perfect model has been the holy grail of researchers in MS . Several models that lead to opticospinal disease a variety of myelin antigens particularly Myelin oligodendrocyte specific protein(35, 36) are known. Two such mouse models (double-transgenic mouse strains [opticospinal EAE mouse]), which spontaneously develop an EAE-like neurological syndrome resembling NMO(37) have been developed by crossing TCR_{MOG} and IgH_{MOG} single-transgenic mice, both onC57BL/6 background. At around 8 weeks of age these mice spontaneously developed demyelinating lesions located in the optic nerve and spinal cord. However these lesion were small (not longitudinally extensive) and there were no detectable AQP4 specific antibodies in the serum or IgG or complement deposition in the lesions. A more definitive model that reflects human pathology more accurately is awaited(38).

1.12 Treatment of NMO

Managing a patient with NMO involves treatment of relapses, strategies for relapse prevention, management of symptoms and rehabilitation

1.12.1 Treatment of Relapses

Treatment recommendations in NMO are largely based on case series or expert opinion, there is no class I evidence to guide long-term management. An acute relapse of NMO (ON or LETM) should be treated as early as possible with intravenous corticosteroids, typically 1 gram of methylprednisolone for three to five consecutive days, after exclusion or treatment of concurrent infection. Therapeutic plasma exchange (TPE) should be considered when clinical symptoms and signs progress (or fail to improve) despite corticosteroid treatment. TPE has been shown to be beneficial in acute CNS demyelinating events unresponsive to steroids. In a randomized controlled, cross-over, double-blind trial 6 of 10 (60%) patients with acute attacks of NMO recovered moderately or markedly after TPE, a response rate greater than that seen in prototypic MS in the same study (39, 40). Typically seven exchanges each of 1 plasma volume done on alternate days are undertaken. I would consider exchange up to 3 months from relapse if significant deficits persist.

1.12.2 Prevention of Relapses

Since the majority of patients with NMO follow a relapsing course, often acquiring substantial disability within two or three relapses, and because immunosuppression appears to reduce relapse rate treatments aiming at relapse prevention should be initiated as soon as the diagnosis of a relapsing NMO is made. Table 1.3 shows currently used immunosuppressive drugs in NMO. It is important to note that no controlled trials dedicated to prevention of relapses in this disorder have been conducted.

Drug	Treatment Regimen and comments	Serious side effects
Azathioprine (41)	Azathioprine is the most widely used drug in NMO. Aim for 2.5 -3 mg/kg body weight. Usually begun along with prednisone 1 mg/kg body weight on alternate days. Steroids are gradually tapered off after 6 months (Case series of	Bone marrow, liver toxicity; Long term potential for malignancies ; potentially teratogenic.

	7 patients)	
Rituximab (Monoclonal antibody against CD20 bearing B cells)(42, 43)	Two 1000 mg infusions 2 weeks apart followed by 6-9 monthly infusions.	Infections. Reports of PML in Rituximab treated patients with SLE; Fetal effects unknown
Mitoxantrone (44)	Mitoxantrone monthly intravenous infusions 12 mg/m2, for 6 months followed by 3 additional treatments every 3 months (Case series 5 patients)	Bone marrow, cumulative cardiac toxicity limits dose; teratogenic
Mycophenolate (45)	2g/day (Case report of 1 patient)	Bone marrow
Intravenous Immunoglobulin (46)	Monthly intravenous infusions of immunoglobulin (400 mg/kg) (Case report of 2 patients	Aseptic meningitis; caution in cardiac renal impairment
Prednisone (47)	Oral prednisone 1 mg/kg body weight on alternate days. Steroids can gradually taper after 6 months and the lowest dose that maintains remission can be continued.	Weight gain, diabetes, infections, gastric bleeds, cataracts, poor wound healing
Other immunosuppressants: Cyclophosphamide, Methotrexate	Therapeutic regimens used in various connective tissue disorders have been used in all major series of patients with NMO	Bone marrow,liver toxicity; Long term potential for malignancies; potentially teratogenic

Table1.3 Drugs used to prevent relapses in NMO

Therapy for NMO spectrum disorders (with relapsing longitudinally extensive myelitis or relapsing optic neuritis) is along the lines as NMO. Whether patients with a single attack of LETM or ON with a positive NMO IgG should be treated remains uncertain. How long treatment should be continued in those patients who have no further relapses with immunosuppressants is uncertain. The long-term side effects of medications have to be weighed against the potential risk of relapses, most of which are severe. Disease modifying drugs (interferons) that are used in MS have not been shown to be helpful Whether NMO-IgG titers could guide therapy is uncertain.

It is important to note that betainterferons used in MS worsens NMO.(48)

1.12.3 Symptom management and rehabilitation

Pain, spasticity, bladder and bowel symptoms and sexual dysfunction need to be tackled. Tonic spasms usually respond to low doses (100-200mg bd) of carbamazepine. Rehabilitation, physiotherapy, mobility and visual aids may be needed. Some patients with severe high cervical cord lesions will need long term home ventilatory support.

1.13. Prognosis of NMO

Most attacks in NMO are moderate or severe; remissions are often incomplete and neurologic disability accumulates in a step-wise fashion. A 'secondary progressive' course is unusual though has been reported. In the Mayo clinic cohort more than half of patients developed severe visual loss in at least one eye and/or inability to ambulate without assistance within 5 years of disease onset. The 5 year-mortality rate in relapsing patients was 32%. All patients died because of respiratory failure associated with attacks of myelitis(11). However this group of patients was seen at a tertiary referral centre at a time when immunosuppressive treatments in NMO were not aggressively pursued and may

therefore not reflect current outcomes. However it is beyond question that attacks of NMO are generally more severe than those seen in MS and disability acquisition earlier than seen in relapsing remitting MS.

1.14 Scope of the thesis

Much of what we know about NMO are extrapolated from the Japanese series and from the retrospective Mayo clinic study over a 30 year period(11) Prospective studies in NMO are rare. The exact epidemiology of NMO is also still uncertain in the western population. Treatments are based on anecdotal or very small case series and often involve multiple drugs. This study therefore aimed to

1. To establish the epidemiology of NMO in the Merseyside
2. To characterise a UK cohort of NMO and their long term outcomes
3. To identify new treatments for NMO

Chapter 2:

Materials and Method

2.1 Studies undertaken

As outlined in the scope of thesis, four separate studies were done:

1. Epidemiology of NMO in Merseyside

   This study was done at the WCNN, and is restricted to Merseyside County.

2. Clinical, laboratory features and long term outcomes of NMO in the UK

   This was a national study including patients from Merseyside.

3. Rituximab treatment of NMO

   The retrospective evaluations on rituximab was an international study involving 7 centres from USA and UK and was done during a one-year fellowship at the Mayo Clinic in Rochester, Minnesota, United States.

4. Mycophenolate treatment of NMO

   This study was done similar to study 3 at the Mayo clinic hospitals, USA but included patients only from the Mayo health care systems

2.2 Methods

Study 1 and 2 was registered in 2003 with the Regional Ethics Committee (**MREC 02/8/082**) Manchester and the research governance committee of the Walton Centre for Neurology and Neurosurgery (WCNN).

The methods of study, study populations, statistical analysis of these are different and therefore are best described separately within the individual chapters themselves.

For studies 1 and 2 after a formal consenting process, a clinical examination was done and bloods were drawn. The MRIs where possible, were analysed at the WCNN. Copies of clinic letters were requested annually and telephone interviews were done(49). Relapses before and after treatments, expanded disability status scores (EDSS) were monitored. Epidemiological data for the denominators were obtained from the website of office of national statistics

2.3 Laboratory testing

Blood samples were stored at the WCNN and were tested partly at the Mayo Clinic (for NMO IgG)(3)and Oxford Radcliffe Infirmary (antiaquaporin-4) using established and previously described methods(25, 50).

2.4 Statistical Analysis:

Summary statistics, paired t tests, Chi-squared tests, Wilcoxon signed rank tests and Kaplan -Meyer survival analysis were done as appropriate using JMP 6. (SAS Institute, Cary, NC, 2005)

2.5. Criteria for NMO and NMO spectrum disorders

I will outline these, which are applicable to all chapters here.

Criteria for NMO (51)
Optic neuritis *and*

Transverse myelitis

And at least *two of three* supportive criteria

1. Contiguous spinal cord MRI lesion extending over 3 vertebral segments

2. Brain MRI not meeting diagnostic criteria for multiple sclerosis

3. NMO-IgG seropositive status

NMO spectrum disorder (51)

Optic neuritis *or*

Longitudinally extensive myelitis

And Presence of NMOIg G or Antiaquaporin-4 antibody

Other criteria will be defined in the appropriate chapters

Chapter 3:
Epidemiology of Neuromyelitis Optica in the County of Merseyside

3.1 Introduction:

There are three population-based studies on NMO from which prevalence rates can be derived. The first study was the nationwide prevalence survey of MS in Japan, which included 82 NMO and 509 MS cases, both with strict diagnostic criteria (52). With an estimated nationwide prevalence rate of 2 per 100,000 population for Japan at that time this NMO/MS ratio would provide an NMO prevalence of 3.2 per 1000,000 (95% CI 0.26-0.40).

The second survey was in Martinique, French West Indies, where there were reported to be French Afro-Caribbean patients with NMO(53). Two of these were said to have MRIs typical of MS; their exclusion would provide an estimated NMO prevalence rate of 3.1 per 100,000 (95% CI 1.5 - 5.5) with 11 cases.

A recent survey from 2003-2004 covered the white and non-white population from Cuba. The prevalence was 5.1 per 1000,000 for the total Cuban population(4).The estimated average annual incidence rate was 0.53 per 1000,000. Neither of these rates differed significantly among whites, blacks, mixed, or non-whites. The number of cases however is far too small to assert the presence or absence of any racial/ethnic predilection for NMO. The prevalence rates by gender demonstrated a much higher rate in females (9.1) than in males (1.2).

Thus although NMO is described worldwide, there have only been a limited number of epidemiological studies, and none in Europe. I therefore decided to examine the epidemiology of NMO in a well defined region of the UK.

3.2 Methods:

Setting:

The Walton Centre serves a population of three million in Merseyside, Cheshire, Lancashire, North Wales, parts of Greater Manchester and the Isle of Man (54). Neurological services are supplied with 26 Neurologists serving individual District General Hospitals (DGH) and their catchment areas (54). It is conventional that any transverse myelitis patient is referred to the visiting Neurologist in the DGH. These patients are almost always transferred across to the Walton Centre for further evaluations. There are of course border zones and patients could attend hospitals or accident emergency departments of hospitals outside the region. To reduce possible over lap I therefore restricted my epidemiological study to the county of Merseyside, which is exclusively served by the centre. (Fig 3.1) To identify cases I searched the WCNN medical records from 2003 to 1995 with the search terms "neuromyelitis optica" or "Devic's disease" or "optic neuritis and myelitis" or "relapsing or recurring myelitis or optic neuritis ". All twenty-six neurology Consultants were contacted for any other possible old or newly diagnosed cases. The Diagnostic criteria for the patients are as described in chapter 2.Only adult patients were included

The following assumptions were made:

1. All cases of NMO would have serious enough symptoms to attend a DGH. They would have been referred to the visiting WCNN neurologists who would have transferred them to the WCNN. The same would have been the case in the unlikely event of slow onset of symptoms, when the primary care physician would have referred to neurologist.
2. The diagnosis of NMO would have been made and recorded as such in the Walton Centre medical records.

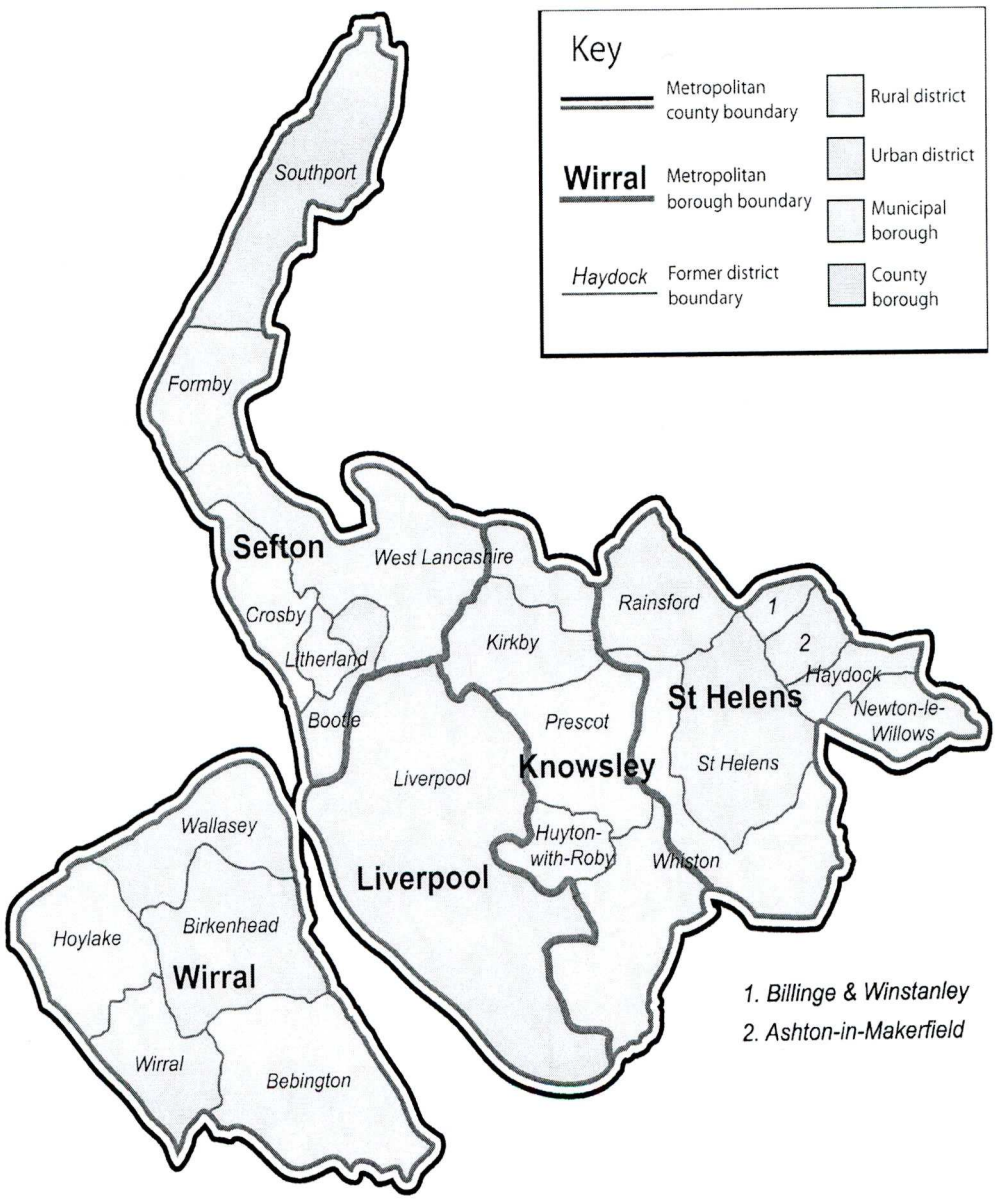


Fig 3.1 The county of Merseyside

3.3 Results:

31st Dec 2008 was considered the census day. The adult population of Merseyside (age more than 16) is 1,145,322 (55). The United Kingdom has an adult population of 46,930,337(55).

Primary care Trusts in Merseyside	Population
Bebington and West Wirral	98,292
Birkenhead and Wallasey	149,453
Central Liverpool	187,837
Ellesmere Port and Neston	64,584
Knowsley	115,942
North Liverpool	81,530
St Helens	140,246
South Liverpool	81,601
Southport and Formby	94,206
South Sefton	131,631
Total	1,145,322

Table 3.1 Population within Primary care trusts of Merseyside(55)

Eight patients with NMO and four with NMO spectrum disorders (all with relapsing transverse myelitis,) were identified during the study from 2003 till Dec 2008. Their clinical details are given as part of the general description in chapter 3 .Three patients with NMO died.

	NMO	NMO SD	Combined
All patients 2003-2008	8	4	12
Alive on 31st December 2008	5	4	9
Incident cases 2003-2008	3	4	7

Table 3.2 NMO and NMO Spectrum Disorders from Merseyside

3.3.1 Prevalence

An estimated prevalence of 7.86/million for combined NMO and NMOSD was calculated. The United Kingdom has an adult population of 46,930,337 and thus giving an estimated 366 patients with NMO or NMOSD across the UK.

3.3.2 Incidence

Seven patients were newly diagnosed (3 NMO and 4 NMO spectrum) over 5 years in the region, since the prospective follow up was begun in 2003 (incident cases) giving an incidence rate of 1.22/million. The United Kingdom has an adult population of 46,930,337 and therefore and an annual incidence of 57 new patients with NMO or NMO spectrum disorders would be expected.

However these are combined figures for both NMO and NMOSD. The individual figures for each of these are given below in table 3.3

	NMO	NMO spectrum Disorders	Combined
Incidence in Merseyside: per million/year	0.52	0.7	1.22
Projected new cases in UK / year	24.59	32.78	57.37
Prevalence in Merseyside/ million	4.37	3.49	7.86
Projected total cases in UK	204.88	163.9	368.78

3.3 Separate and combined figures of NMO and NMOSD in Merseyside.

3.3.3 Gender and ethnic differences:

Women accounted for 78% of patients. The majority of patients were white (88%, table 3.4) Only one patient was non white, a black woman, resident in the region since 2000, with the onset of illness while in Nigeria in 1996.

	Combined NMO and NMOSD % (n)	Population of Merseyside (%)	Population of United Kingdom (%)
Gender: Male	22(2)	48	48.7
Female	78(7)	52	52.3
Ethnicty: White	88 (8)	97.6	91.31
Black	12 (1)	0.36	2.18
Asian	0	0.58	4.8
Mixed	0	0.8	1.27
Others	0	0.66	0.44

Table 3.4.Gender and ethnic distribution (shown as percentages) of NMO patients compared with the Merseyside population and the whole UK Population

3.4 Discussion:

A nationwide wide epidemiological study though desirable is not possible as there is a referral bias in the patients seen across the United Kingdom – not all patients being referred or seen as part of this study. However I attempted this in the selected catchment area of the Walton Centre - a fairly well defined geo-political area.

I have estimated the crude prevalence and incidence of NMO and NMOSD in Merseyside using hospital based statistics. Such data are rare in literature particularly in regions with high number of Caucasian population. We also estimate the prevalence and incidence of NMOSD which has not been documented before. The figures of NMO are comparable to that of other reports, but when combined with those of NMOSD give a much higher numbers, increasing the burden of disease. As NMO and NMOSD follow the same morbidity and clinical course and as there are no treatment differences these larger numbers have great significance when planning specialist services.

These results also confirmed previously reported findings of a higher female frequency of NMO in case series. In the population-based study in Martinique, all of the 13 prevalent

cases were French Afro-Caribbean women(53). In the nationwide prevalence study in Japan, 52 (63.4%) of the NMO cases were women.

In the Cuban study prevalence rates by gender demonstrated a much higher rate in females (9.1) than in males (1.2)(4). But there were no difference between whites, blacks, mixed, or non-whites. The numbers in our study sample are too low to make meaningful statistical comparisons.

However there are several important limitations to this estimate, which can be at best a minimum value. The number of cases is far too small to assert the presence or absence of any racial/ethnic predilection for NMO. The three presumptions made above may not be accurate. Though I am reasonably confident that all cases with an optico-spinal syndrome or severe transverse myelitis would have been seen by the neurology services, the same cannot be assumed for optic neuritis which may not be referred on to the neurologist by the ophthalmologist or brought into the centre for further tests. Though untreated NMO has an average annual relapse rate of about 2 /year, it is possible that the second relapse, the commonest reason for referral for further neurological evaluation may not have occurred yet. Due these caveats I believe that my figures of incidence and prevalence are the minimum. It is important to remember that children were not included in this study

Chapter 4.
Clinical, Laboratory Features and Long Term Outcomes

4.1 Introduction

Neuromyelits optica is an uncommon disorder. Though there are many case reports from the western countries, there are very few series of patients with substantial numbers and none with prospective follow up. The largest series to date is that from the Mayo clinic reported in 1999, which reviewed 71 patients seen at the Mayo Clinic between 1950 and 1997. A French group retrospectively studied 13 patients (56) and later (57) presented data on 30 patients. A further French retrospective study looked at therapies of 26 patients with NMO followed in five French neurological departments. An Italian study of 46 patients from 15 centres also retrospectively reviewed data and surmised their experience (58). The only study form the United kingdom was a retrospective case record based study in1996 that reviewed 12 patients attending The National Hospital of Neurology and Neurosurgery, Queen Square and Moorfield's Eye Hospital between 1986 and 1994.(59)

Retrospective data have many well known innate inadequacies- selection and recall bias, lack of follow up, non availability of records and investigations. Prospective studies are harder to organize, time consuming but may provide more accurate information of long-term outcomes.

In 2003, at the outset of this study, NMO was still a 'debated' diagnosis. Diagnostic criteria were not widely accepted and patients were often classified as optico - spinal forms of MS. I therefore attempted to first identify a cohort of all forms of optico-spinal demyelinating syndromes and then sub classify and follow them up prospectively.

4.2 Materials and methods

4.2.1 Identification of Study population:

The UK Prospective Cohort study population was obtained by two methods:

1. British Neurological Surveillance Unit (BNSU)

The British Neurological Surveillance Unit was set up in January 1993 with the aim of co-ordinating and improving the ascertainment of rare neurological disorders in the United Kingdom by using a system of nation-wide active surveillance. The unit provides a service for individual investigators who must first submit possible studies to a scientific advisory committee. Once accepted the condition is listed on a report card which is sent to every member of the British neurological community every month. The cards are easy to use, and all the reporting neurologist has to do is tick a box indicating whether a case has (or has not been) seen. At the end of every month the individual investigators then initiate further follow-up by contacting the reporting neurologists(60).

I contacted all neurologists in UK through the British Neurological Surveillance Unit (BNSU).The notification forms were then compiled by the BNSU and returned to me. I then contacted the individual Consultant. The Consultant would then request the patient's consent for recruitment into the Study. The primary investigator would then visit the Hospital, review records, MRI scans, meet the patient at the Hospital or at their home.

CRITERIA FOR REPORTING PATIENTS TO THE BNSU :

Adults (age > 16 years) with Optic Neuritis and transverse myelitis without a typical (61) brain Magnetic resonance imaging (MRI) for multiple sclerosis

These patients were broadly called optico-spinal demyelinating diseases(OSD). *These criteria were necessarily broad to include all possible optico-spinal demyelinating cases.*

Adults with typical multiple sclerosis, single episode of optic neuritis or isolated transverse myelitis or an obvious non-demyelinating cause for the spinal cord and optic nerve disease were not to be referred.

2. Medical Record search at the Walton Centre

This was done as outlined in Chapter 2

3. Additional patients included in the study

With the availability of antibody testing (NMO IgG/AQP4-Ab) the diagnosis of NMO has been extended to patients who have either optic neuritis or myelitis if they have NMO IgG /aquaporin-4 antibody. Such patients – NMO spectrum disorders -behave like NMO clinically with a relapsing course and therefore have been included in the analysis of NMO /NMO spectrum patients, but not in the section on cases with optico-spinal presentation.

4.2.2 Analysis of data:

Patient classification (Fig 4.1):

Based on clinical-radiological profiles, NMO antibody status and follow up, all OSD patients were broadly divided into two categories:

1. Neuromyelitis optica.
2. Non-NMO optico spinal demyelination (NNOSD)

The additional criteria for NNOSD are:

Transverse myelitis shorter than 3 vertebral segments *and*

NMO antibody is negative.

The NNOSD category of patients was subdivided into two:

1. Patients with a pure optical and spinal presentation, who on follow up developed typical relapsing-remitting, primary progressive or secondary progressive multiple sclerosis.(62)
2. Patients who still remain as optical and spinal demyelination and did not develop typical MS of any subtype with (ie associated with brain MRI changes satisfying Barkhof's criteria). These were called optico-spinal demyelination Unclassified (OSD-U)

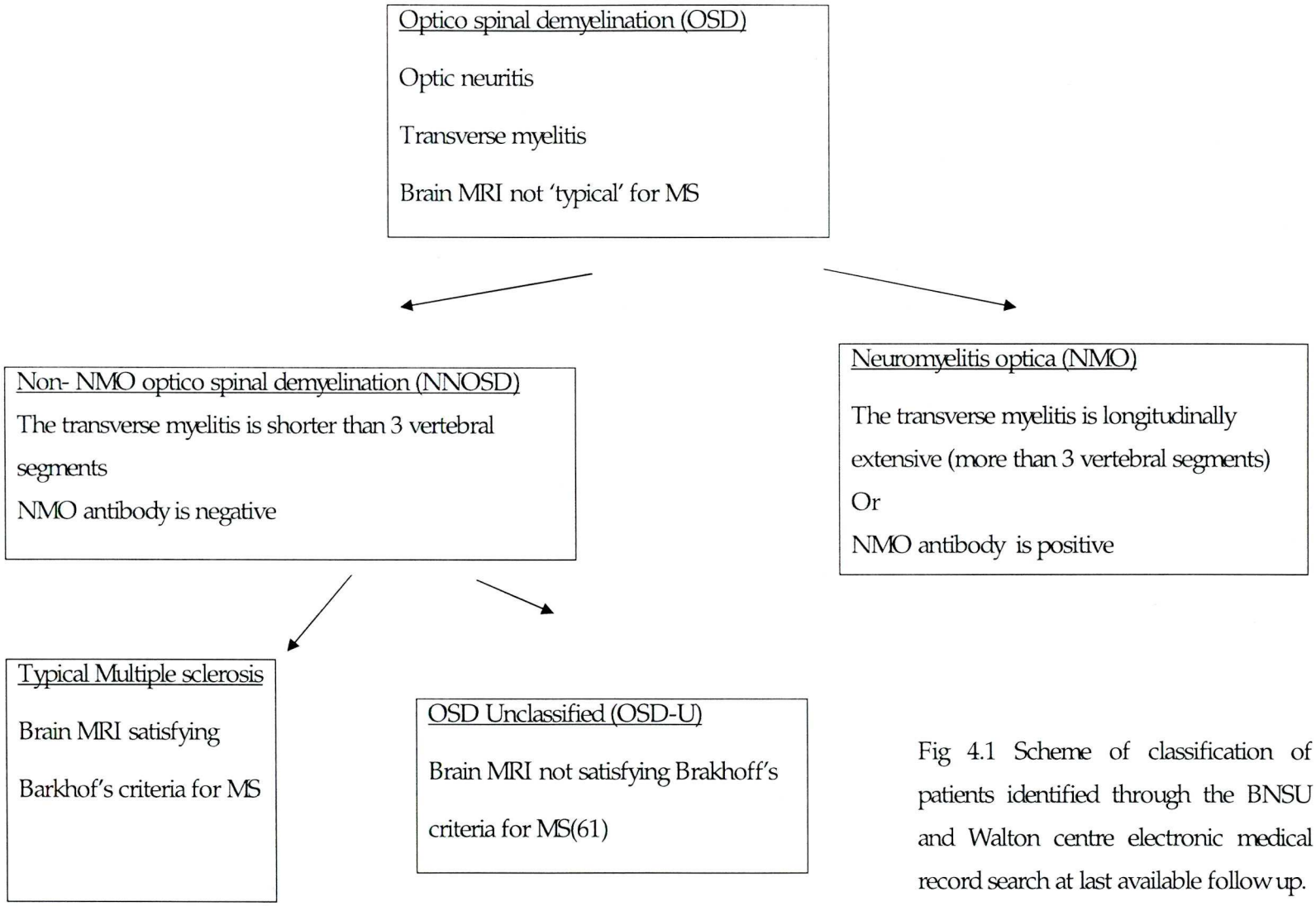


Fig 4.1 Scheme of classification of patients identified through the BNSU and Walton centre electronic medical record search at last available follow up.

4.3 Results

The classification of patients is summarised in Fig 4.1. 128 patients were evaluated for inclusion into the study. 67 patients satisfied the inclusion criteria for OSD. 61 patients were excluded, as they did not satisfy criteria. These included patients who had single episodes of demyelination or relapsing myelitis or optic neuritis (antibody testing was unavailable) or patients with alternative diagnosis.

Of the 67 patients with OSD 42(63%) were women and 25 (37%) men.
The median duration of follow up was 38 months (0-71 months). Based on clinical-radiological profiles, NMO antibody status and follow up, all OSD patients were broadly divided into two categories: 34 (51%) had NMO and 33(49%) had NNOSD.

NMO spectrum disorders

With the increasing understanding of NMO, and NMOSD, I included 8 patients with NMOSD (which behave similar to NMO clinically) referred to WCNN in the NMO group, raising the final number of patients with NMO or NMOSD to 42

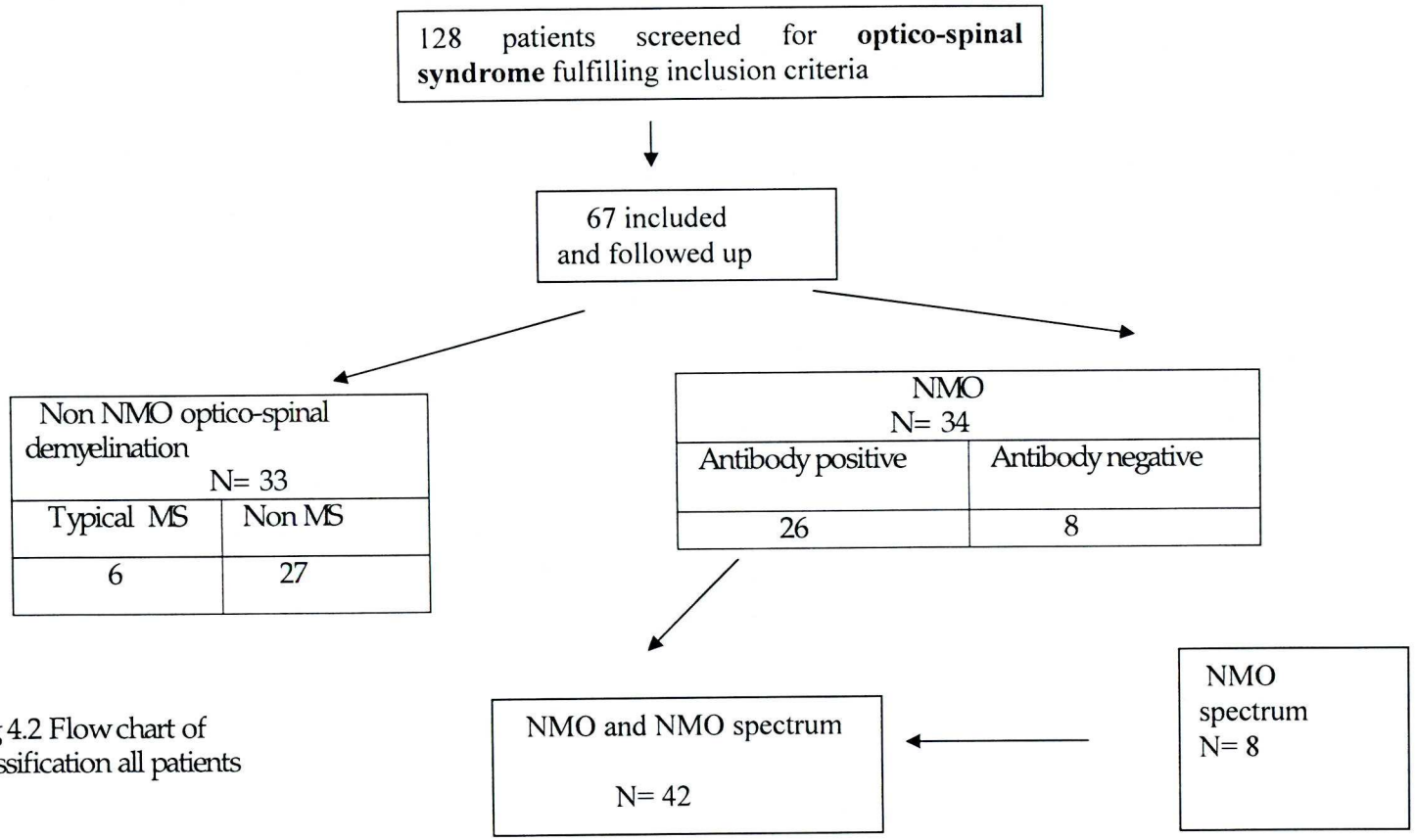


Fig 4.2 Flow chart of classification all patients

4.3.2 Neuromyelitis optica and NMO spectrum disorders

Forty-two patients had NMO/NMOSD. Thirty six of these patients had an optical and spinal syndrome and were obtained from the national study. Eight patients were OSD (Seven with relapsing myelitis and one with relapsing optic neuritis). Thirty-four (81%) were antibody positive and 8 (19%) were negative. Thirty-one of the 42 patients (74%) are women. Forty five percent of men were antibody positive compared to 94% women. The epidemiological data of the patients are presented in table 4.4.

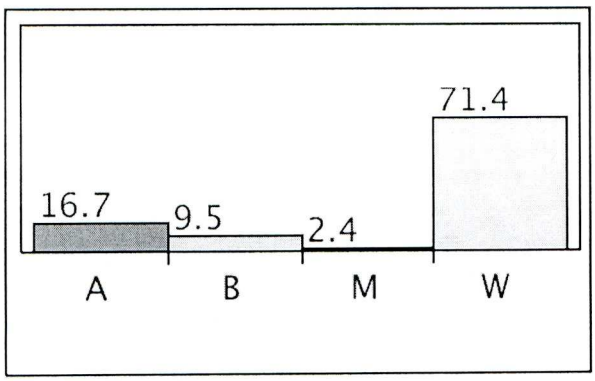
4.3.2.1 Gender:

Feature		All NMO and NMOSD (n=42)	NMO and NMOSD antibody positive (n=34)	NMO and NMOSD Antibody negative (n=8)	Significance	Test of significance
Gender (%)	Men	11 (26)	5 (45)	6(55)	P=0.005	Fishers exact
	Women	31(74)	29(94)	1(6)		
Race (%)	White	30 (71)	22(73)	8(27)	NS	Fishers exact
	Non white	12 (29)	12(100)	0		
Age at onset median (range)		40.8 (11-76)	39 (11-76)	48 (16-61)	NS	Mann-Whitney U

Table 4.1 Demographic data of 42 patients with NMO or NMOSD

4.3.2.2 Ethnic differences

Twelve of the 42 patients were non white. Fig 4.2 shows the ethnic distribution of all the patients comparing them to the UK distribution of ethnic minorities.



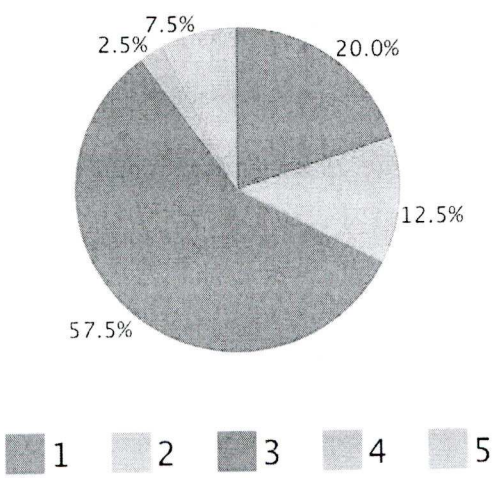
	Count (%)	Ethnic distribution in UK (%)
Asian (A)	7(16.7)	4.8
Black (B)	4(9.5)	2.2
Mixed ethnicity (M)	1(2.4)	1.3
White (W)	30(71.4)	91.3
Other		0.44
Total	100	100

Fig4.2 Ethnic Distributions in NMO in the UK

White patients accounted for 71.4% of the cohort. However they account for 91.3% of United Kingdom population. On the contrary Asian, black or mixed ethnicity patients accounted for more than expected.

4.3.2.3 Index clinical event

The index (ie the first) clinical event was either optic neuritis in 32.5% and transverse myelitis in 57.5% and a combination in the rest (10%). More specifically, unilateral optic neuritis occurred in 20%, bilateral optic neuritis (12.5%) Fig 4.3.



1. Optic neuritis -unilateral
2. Optic neuritis -bilateral

3. Transverse myelits
4. Unilateral optic neuritis with myelitis
5. Bilateral optic neuritis with myelitis

Figure 4.3 The index event of NMO

4.3.2.4 Monophasic and relapsing subtypes.

All patients had a relapsing course. The number of relapses before and after immunosuppressant treatment is given in section on response to treatments

4.3.2.5 Time to second event:

I estimated the time between the first and second event in 40 patients (e.g.: If optic neuritis was the first event, the time to next episode of either ON or TM). The median time to the second event was 7.75 months (1.98 to 60). Date of the second episode was uncertain in 2 patients.

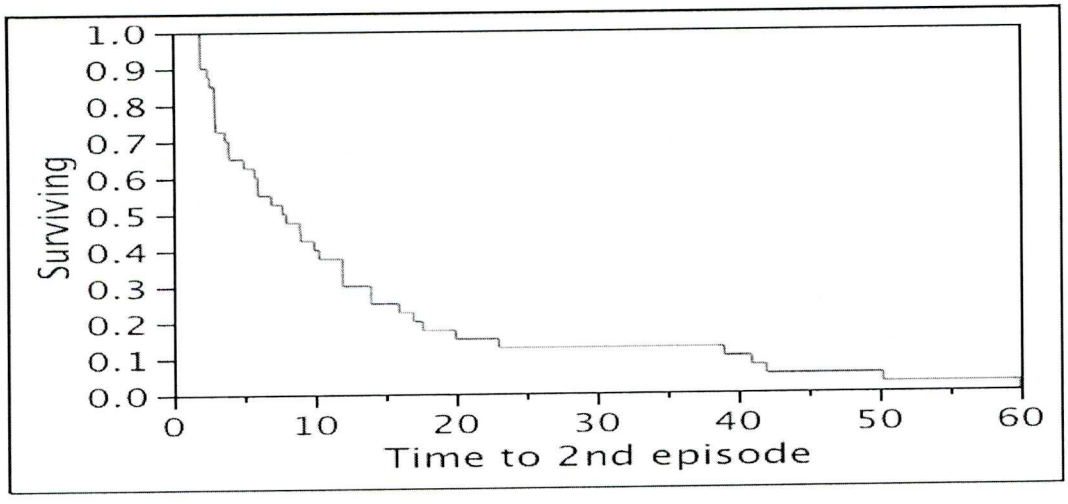


Fig 4.4. Kaplan–Meier survival curves for time to 2nd episode in 40 patients

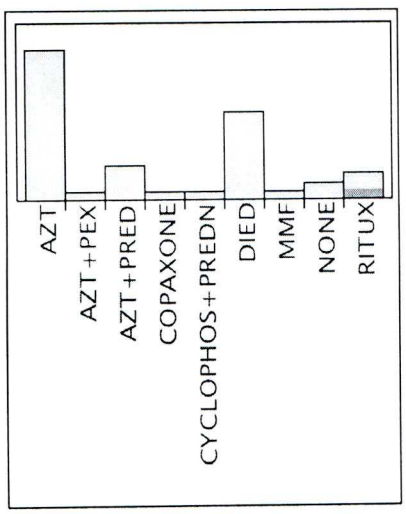
Summary Group	Number failed	Number censored	Mean	Std Error
Combined	40	0	12.8435	2.25055

Group	Median Time	Lower95%	Upper95%	25% Failures	75% Failures
Combined	7.7536	3.9754	11.992	3.0226	13.996

Quantiles

4.3.2.6 Treatments used in NMO

Azathioprine with or without steroids was the most favoured current treatment (fig 4.4) Two patients are not on treatment- one remains in remission and one is deciding on the drug that she wishes to start.



Level	Count	Percents
AZT	17	42.5
AZT+PEX	1	2.5
AZT+PRED	4	10.
COPAXONE	1	2.5
CYCLOPHOS +PREDN	1	2.5
DIED	10	25
MMF	1	2.5
NONE	2	5
RITUX	3	7.5
Total	40	100

Fig 4.5 Distributions of current treatments for NMO in 40 patients.
AZT (Azathioprine), PEX (Plasma exchange), Pred (Prednisone) cyclophosph (cyclophsophamide), MMF (mycophenolate) and Ritux (rituximab)

4.3.2.7 Response to treatments

I calculated the duration of disease before and after starting *any* immunosuppressant treatment and the number of relapses that occurred during these periods , irrespective of the type or number of drugs they were on. However the precise number and dates of relapses were available only in 33 patients. The median annualised relapse rates before treatment for these 33 patients was 1.6 (0.16-45) and post treatment was 0.19(0-5.5) at a median follow up of 2.7(0.04-5.9) years after entry into study (p= 0.0019, Wilcoxon signed rank test)

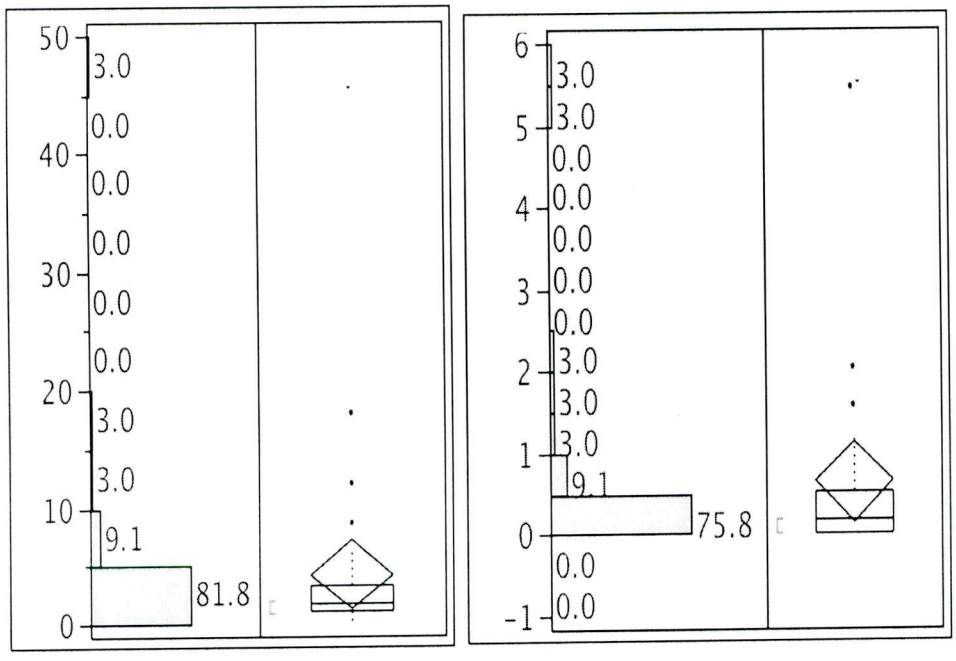


Fig 4.6 Annualised relapse rates before any disease modifying treatment. The figure on the left is the pre treatment and that on the right is post treatment. The horizontal axis denotes the percentage of patients and the vertical axis the relapse rate itself.

The wide and high range of relapse rates is due to the short durations before and after starting treatment. To avoid this bias patients who had a pre or post treatment duration of less than one year was excluded; then,the Annualised relapse rates before treatment was 1.4(0.38-5.9) and post treatment was 0.19(0-2) at median follow up of 2.7(0.04-5.9) years (n=24; p< 0001, Wilcoxon Signed rank test).

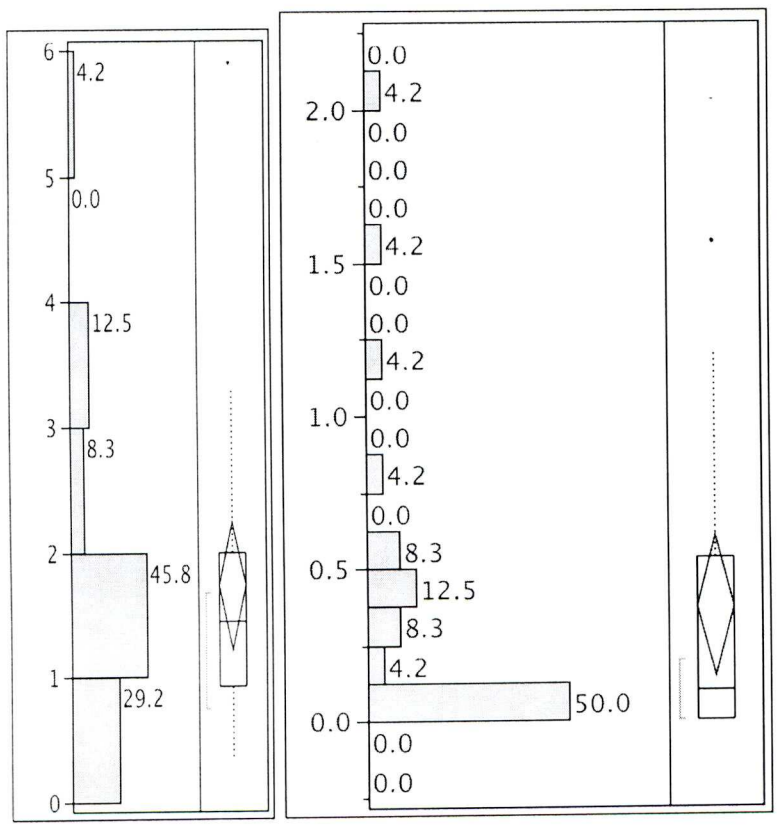


Fig 4.7 Annualised relapse rates before any disease modifying treatment. The figure on the left is the pre treatment and that on the right is post treatment. The horizontal axis denotes the percentage of patients and the vertical axis the relapse rate itself.

4.3.2.8 Disability

The median expanded disability status scale (EDSS) at the onset of the study was 6.5(2.5-8.5) and at last follow up 6.75(1.5-10) (Fig 4.7) (p=0.15, Wilcoxon signed rank test). This

change was over a median period 2.8years (0-5.9) and median duration of disease of 6.9 years (0.2-31)

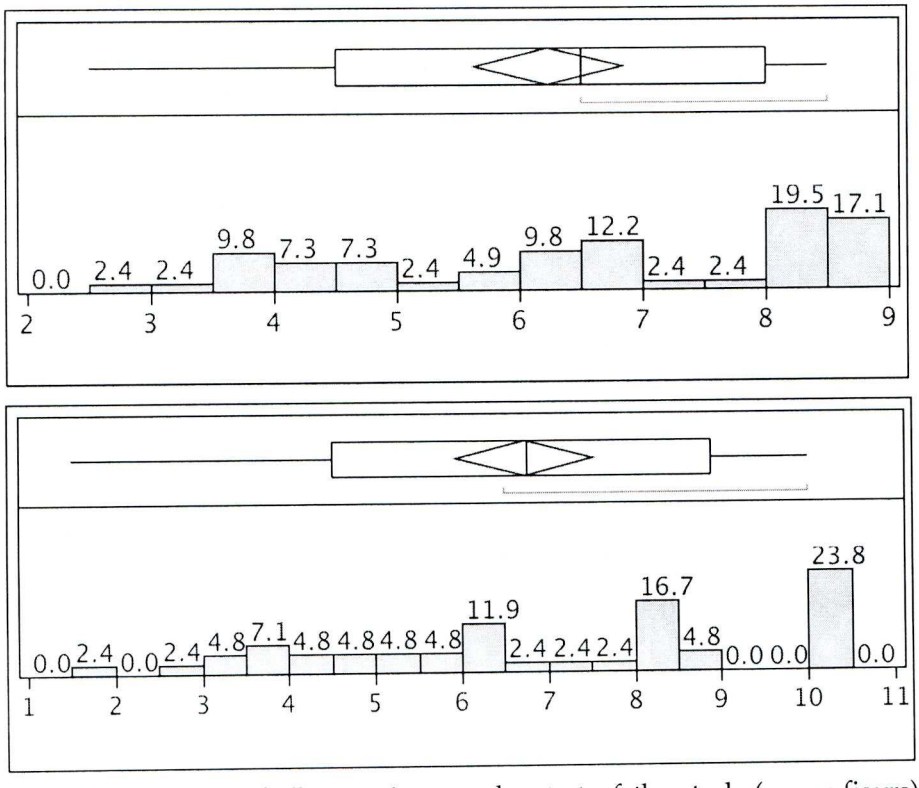


Fig 4.8 The EDSS of all 42 patients at the start of the study (upper figure) and at last follow up (lower figure) the horizontal axis denotes the EDSS; the height and numbers at the top of each bar indicate the percent of patients with that EDSS.

4.3.2.9 Time to disability

I estimated the median time to development of permanent disability (as defined by residual disability before the next relapse or at 6 months if there are no further relapses) as 0 months (0-89); i.e. the first event itself. 75% patients would have developed a fixed disability by 6 months.

I similarly estimated that episode that caused the permanent disability would be the first event in 28 (67%), second in 6(14%) third in 7(17%) fifth in 1(2%)

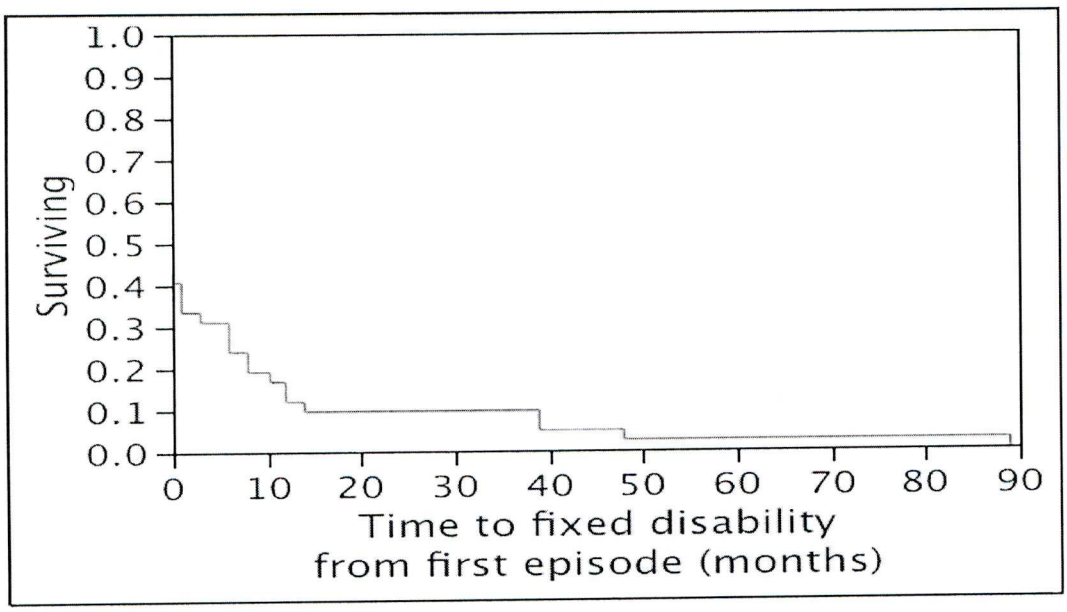


Fig 4. 9 Time to event: Time to fixed disability from first episode (months)

Summary Group	Number failed	Number censored	Mean	Std Error
Combined	42	0	7.22262	2.63047

Quantiles Group	Median Time	Lower95%	Upper95%	25% Failures	75% Failure
Combined	0	0	1	0	

Time to fixed disability from index events	Survival	Failure	SurvStdErr	Number failed	Number censored	At Risk
0.0000	1.0000	0.0000	0.0000	0	0	42
0.0000	0.4048	0.5952	0.0757	25	0	42

1.0000	0.3333	0.6667	0.0727	3	0	17
3.0000	0.3095	0.6905	0.0713	1	0	14
6.0000	0.2381	0.7619	0.0657	3	0	13
8.0000	0.1905	0.8095	0.0606	2	0	10
10.3500	0.1667	0.8333	0.0575	1	0	8
12.0000	0.1190	0.8810	0.0500	2	0	7
14.0000	0.0952	0.9048	0.0453	1	0	5
39.0000	0.0476	0.9524	0.0329	2	0	4
48.0000	0.0238	0.9762	0.0235	1	0	2
89.0000	0.0000	1.0000	0.0000	1	0	1
Combined						

4.3.2.10: Mortality

Ten patients have died during the study period in the NMO group. Fig 4.5 All patients were on some form of immunosuppression. The median time to death from onset of illness in these 10 patients were was 6.1 years (2 months to 16 years). Unfortunately details of the circumstances of death are not available in all. No patients died in the NNOSD group.

	All NMO and NMO-S (n=42)	NMO and NMO-S antibody positive (n=34)	NMO and NMO-S Antibody negative (n=8)	Significance	Test of significance
No of Death (%)	10(24)	7(70)	3 (30)	0.28	Fisher's exact
Men		2 (20)	2(20)		
Women		5(50)	1(10)		

Table4.2: No of deaths in NMO cohort stratified by antibody status.

CAUSE OF DEATH	NUMBER OF PATIENTS
Infection	3
Relapse	3
Accidental overuse of opioids	1
Pulmonary embolism	1
Cause uncertain	2

Table 4.3: Cause of death in NMO

Using Kaplan- Meier survival statistics I estimated the expected median time to death as 16 years from onset of the first episode even though 95% of patients were on treatment (fig 4.5) 7 of 34 (20%) antibody positive and 3 of the seven (42%) antibody negative patients died (p =0.28) Fig . Two of the NMO antibody negative patients died very shortly after the onset of the disease (2.46 and 9 months) due severe brainstem relapse.. Antibody negative group had shorter median time to death (fig4.10)

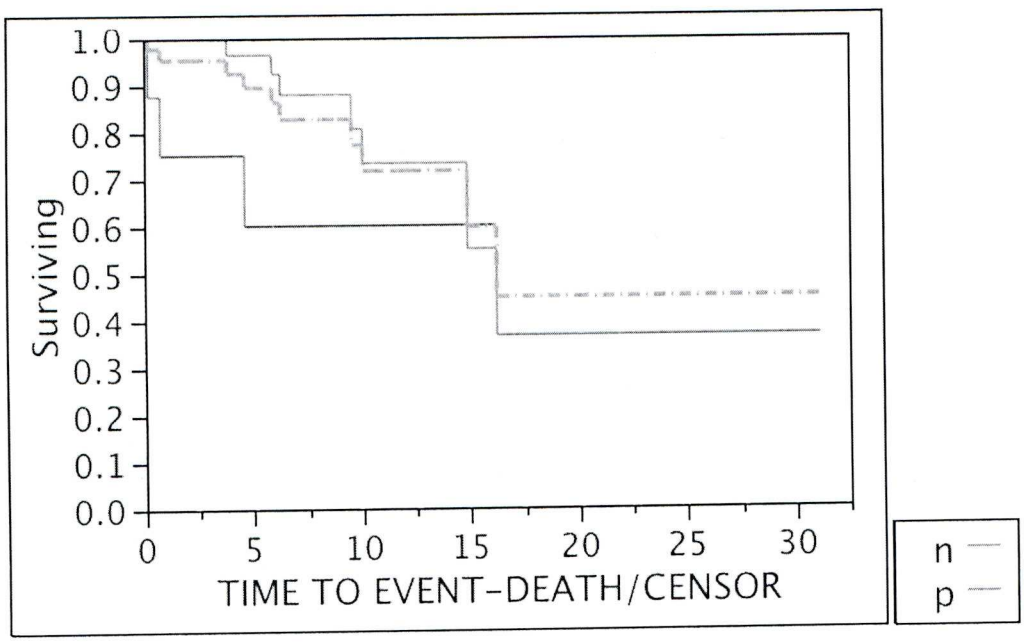


Fig 4.10 Time to death: Kaplan- Meier (Product-Limit) survival of all patients (interrupted grey) and stratified by NMO antibody status. The red line is antibody negative group and blue, antibody positive.

Summary

Group	Number failed	Number censored	Mean	Std Error
n	3	5	3.59788 Biased	0.78226
p	7	27	13.7571 Biased	0.94652
Combined	10	32	13.2454 Biased	0.9219

Quantiles

Group	Median Time	Lower95%	Upper95%	25% Failures	75% Failures
n	.	0.2053	.	4.6379	.
p	16.257	10.081	.	10.081	.
Combined	16.257	10.081	.	10.081	.

Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	0.6848	1	0.4079
Wilcoxon	4.9798	1	0.0256

Combined

4.3.2.11 Co existing autoimmune diseases and autoantibodies

Co existing autoantibodies (AAB) were present in 18/30 patients 60%. (Table 4.6 and 4.7)

10(24%) had a manifest autoimmune illness and one had a thymoma.

Antibody	No of patients
Rheumatoid factor	1
ANA	13
ds-DNA	3
SSA(Ro)	4
SSB (La)	1
Scl 70	1
Jo 1	1
c-ANCA	1
Smooth Muscle	1
Acetylcholine receptor antibody	1
Thyroglobulin	1
Anti cardiolipin antibodies IgG	4
Anti cardiolipin antibodies IgM	3
Celiac Screen	3
Antiganglioside antibody	1

Table. 4.4: Co- existent autoantibodies in NMO. SSA and SSA-B: Sjogrens syndrome A, and B, Jo-1: associated with inflammatory myopathy), Scl-70: scleroderma antibody

against topoisomerase, dS-DNA: double stranded DNA, ANA: antinuclear antibody, ANCA: anti neutrophil cytoplasmic antibody

Celiac disease	3
Psoriasis	2
Hypothyroidism	2
Systemic lupus erythematosis	1
Rheumatoid arthritis	1
Non specific possibly immune arthritis/arthralgia	3
Pernicious anemia	1
Insulin depenedent diabetes mellitus	1

Table 4.5 Co existent autoimmune disease in patients with NMO

Three patients had celiac disease one of whom was antibody negative.(63). In two patients gastrointestinal symptoms prompted testing for celiac disease, while in the third, the diagnosis of NMO prompted testing for celiac antibodies as the patient was aymptomatic. Diagnosis was confirmed by biopsy in all. All remain on azathioprine in remission of both NMO and celiac disease.

4.3.2.12 Oligoclonal bands in the spinal fluid.

Oligoclonal bands (OCB) were absent in 28/33 (85%) where results were available. 78% of patients positive for NMO antibodies had no OCB.

		All NMO and NMO-S (n=33)	NMOand NMO-S antibody positive (n=25)	NMO and NMO-S Antibody negative (n=8)	Significance	Test of significance
Oligoclonal bands in the CSF(%)	Present	5 (15)	3(60)	2 (40)	P =0.35	Fishers exact
	Absent	28 (85)	22 (78)	6(22)		

Table 4.6 Oligoclonal bands in NMO and NMO SD patients

4.3.3 Non NMO Optico-spinal demyelination

Thirty-three patients of the 67 were not NMO. Six of these developed MS. Twenty seven were classed as OSD-U.

Feature (%)		No of patients (%) with NMO (n=34)	Number of patients (%) with Non NMO OSD (n=33)	Significance	Test of significance
Gender	Men	8 (13)	17(51)	p=0.0245	X^2
	Women	26(77)	16(49)		
Race	White	23(67)	24(71)	NS	X^2
	Non white	11(33)	9(19)		
Age at onset median (range)		39(16-69)	34(18-50	NS	Mann-Whitney U
Family history of demyelinating Illness	Present	3(8)	1(3)	NS	X^2
	Absent	31(92)	31(97)		
Coexistent autoimmune illness	Present	10(41)	5(16)	NS	X^2
	Absent	24(69)	27 84)		
No of Deaths		10 (30)	0 (0)	P<0.0069	Fishers exact

Table 4.7 Differences between NMO/SD and NNOSD

Men and women were present almost equally in this group. The median EDSS at onset and at last follow up was both 3 in NNOSD compared to 6.5 and 6.75 in the NMO group No patient in this group died. Oligoclonal bands were absent in 67% patients. Since the scope of the thesis was the study of patients with NMO, a detailed analysis of this subgroup is not presented here.

4. 4 Discussion:

4.4.1. Gender differences

Seventy four percent of the cohorts were women. This is similar to the Italian (80%), Mayo (83%) studies. Eleven out of 12 patients in the previous UK study were women. Most autoimmune diseases are more common in females. Though there seems to be significant difference between the numbers of men in the antibody positive versus negative group, the low numbers make this conclusion uncertain.

4.4.2. Ethnic differences

Our findings are consistent with widely held view that NMO is more common in non-Whites. In the previous UK study seven of the 12 patients were non-White. In the Mayo clinic study 6/71(8%) were non-White. However there is likely to be confounders in this observation. As the belief that NMO is commoner in non-Whites is widely held, more patients with optico-spinal presentation would have been diagnosed (and referred to the study) as NMO by neurologists than whites who may have been diagnosed with MS.

It is interesting that in the hospital-based study of the Merseyside population (chapter 3) no over representation was seen. Similiarly, the population based Cuban study did not find an ethnic differences. Further study is needed to confirm this new view. Though MS may be less common in Asians and Blacks, NMO might not be more frequent than MS.

4.4.3 Monophasic and relapsing NMO

There were no monophasic cases in this study. All patients relapsed on longer follow up.

Wingerchuk etal classified NMO into monophasic (simultaneous or separate occurrence of ON or TM and no further events) and relapsing type(11). The monophasic type occurred in about 32% cases in their series. But they acknowledge that no monophasic case was diagnosed since 1988 i.e. from 11 years before their study. In their retrospective study the mean follow up for monophasic group was 16.9 years (minimum 3 years).

It is debatable whether monophasic NMO exists. It seems unlikely, though not impossible that an antibody mediated disease with would confine itself to one or two events. It is likely that simultaneous occurrence of optic neuritis and myelitis with no further events (30% of the in the Wingerchuk series) may be a subtype of acute disseminated encephalomyelitis if they are antibody negative. It is also interesting that the median time to second index event in the monophasic group in that study was 5 days only implying that both index events are manifestations of a single acute event rather than two separate ones.

These arguments would mean that NMO is always a relapsing disorder. It could also imply that there is no need to initiate immunosuppressive treatment in patients who have an antibody negative monophasic illness.

4.4.4 Time to second attack in NMO

I estimated the time between the first and second event in 41 patients. The median time to the second event was 7.8 months (1.98 to 60) [4.9 (1.9-50) in the antibody negative group and 9(2-59) in antibody positive group]. This has treatment implications. Though it is generally agreed that all patients with confirmed relapsing NMO should be treated with immunosuppressive medications (based on anecdotal evidence) it is still uncertain whether patients with NMO-SD with a single event should be treated in the same way. This is understandable. Both the physician and the

patient are likely to be uncertain about the need for possibly life-long immunosuppression based on the presence of a blood marker.

It has been shown that 55% of isolated longitudinally extensive myelitis and 80% of those with relapsing optic neuritis with NMO IgG will relapse by one and nine years respectively(30, 64). Our findings would support the view that treatment should be initiated, as a relapse seems highly likely in all untreated patients, where the antibody is positive(30, 64). This combined with very high degree disability, acquired by 15 months or by the third episode itself in 90% patients makes preventative treatment important in those patients where a relapse can be predicted by presence of the NMO antibody. However it can be debated that a selection bias explains these results– with only patients who relapsed being referred to the study - and the prediction of a relapse is self-fulfilling.

4.4.5 Treatment response

Our results are consistent with the general view that disease modifying treatment i.e. immunosuppressants tend to lower the rate of relapses. The lack of controlled trials makes these observations prone to errors. The median annualised relapse rates before treatment was 1.6 (0.16-45). With any kind of disease modifying treatment the relapse rates improved to 0.19(0-5.5) at a median follow up of 2.7(0.04-5.9) years for 33 patients ($p< 0001$, Wilcoxon signed rank test). These improvements are comparable to those achieved with rituximab or mycophenolate (chapter 5 and 6). No treatment seems to have been instituted in one patient despite a long history of illness. One patient with a relatively new diagnosis is still deciding on the treatment. In many patients the initial drug was ineffective or induced side effects leading to a change and this was needed several times in some. One patient is now on glatiramer acetate. A single case report supports this attempt(65). She had relapses and did not tolerate azathioprine, mitoxantrone, mycophenolate and rituximab.

There are several major limitations to estimating relapse rates in retrospect:

1. Finding the exact stopping dates and start of new medications turned out to be extremely difficult, making attempts to identify which treatment was more effective, fruitless.

2. Similarly the number of relapses that occurred pre and post treatment was often difficult to ascertain. Recall bias was an important confounder.

3. Similarly the delays from the onset of symptom to be seen by the tertiary care, treatment at the primary care level itself with steroids for suspected symptoms of relapse (possibility pseudo-relapses being unnecessarily treated) and patients perception of what a relapse is confounds accurate relapse characterisation.

4. Many patients with NMO are steroid dependent and taper of steroids often leads to recurrences of symptoms. Two patients who have had fifteen to twenty relapses over a two to three year period is an example.

5. Another problem in such analysis using annualised relapse rate is often the short time interval between the onset of the disease to treatment. For example if an episode transverse myelitis was immediately suspected to be an NMO spectrum disorder and proven correct with antibody testing and the Physician initiated treatment with no relapses in the subsequent year then the pre-treatment *annualised* relapse rate would 12.5 [1 divided by 0.08 years (1 month)] and the post treatment relapse rate would be 0!

6. Some issues are indigenous to the NHS. The reasonably effective UK primary health care system does filter out many patients with relatively minor relapses by providing treatment, before they reach district hospitals where neurologists work. This is unlike the US healthcare system where primary healthcare Physicians are bypassed more often than not. Therefore documentation of clinical symptoms and details of relapses in tertiary care hospitals seem to be much higher and

extracting accurate data more easier as evidenced by the chapters on rituximab and mycophenolate which were done while I was in the United States. Nevertheless I feel the values of pre and post treatment annualised relapse rates are reasonable estimates.

4.4.6 Mortality and Disability

Disability in NMO is believed to be acquired by attacks as opposed to the gradual accumulation in progressive MS. At a the median follow up of 2.8 years since the onset of the Study, the median EDSS changed from 6.5 to 6.75. Even if the 10 patients who achieved an EDSS of 10(death) were excluded the EDSS at onset and at last follow up remained 6.5.

The use of EDSS as an effective tool for assessing disability in spinal cord and optic nerve predominant disease can be contested. Specialised scoring systems like the ASIA (American Spinal Injuries Association) score used for spinal cord injuries might be more appropriate. A similar scoring system specific for visual loss could be used for the eye. However as EDSS is well validated, commonly used and easily interpreted by neurologists this was deemed more appropriate.

There are several limitations to my EDSS scores. Many of the EDSS scores have been estimated from observation from hospital notes and subsequently by telephone, the latter method having been validated to be comparable to physical exam(49). Some were obtained while the patients were in relapse and hence the improvement would have been 'regression to the mean'. Nevertheless we feel that our observations are valuable and provide some light into the progression of the disease in this group of patients. Our Data compares well with the other documented series. The mayo clinic series indicate that 50% of patients are wheel chair bound or have vision poorer than 20/200 at 5 years(11). The predicted median survival of patients in the Mayo series is 17.6 years compared to

ours of 16 years. Despite universal treatment with some form of immunosuppression, only modest improvements in survival seem to have been achieved. This comparison could be skewed as the Mayo series was retrospective with incomplete follow ups.

4.4.7 Anti Aquaporin- 4 antibodes:

We found that 81% of patients have anti AQP4 antibodies. The rigorous application of the diagnostic criteria and use of newer methods to detect the antibodies might have improved the sensitivity of the tests to detect the antibodies compared to other series. The patients who were antibody negative could be so for many reasons. These include treatment with immunosuppressants or intravenous steroids which reduce the levels(66), incorrect diagnosis or true 'antibody negative' NMO. The latter brings into the possibility that there might be yet unidentified antibodies involved in the pathogenesis. The antibody negative groups had a shorter median time to death and treatment of this group rigorously might be required. The small number of patients in the antibody negative group makes results difficult to interpret and the differences between antibody positive and negative groups will be borne out only in larger Studies.

4.4.8 Co existing autoantibodies and autoimmune illness

Coexistence of autoimmune illnesses is well known in NMO(67). In this series we identified several autoimmune illnesses and autoantibodies. Three patients had coeliac disease.

Treatments for managing both NMO and coexisting autoimmune illnesses are similar i.e azathioprine, methotrexate, cyclophosphamide, mycophenolate etc. It is possible a proportion of patients with a tendency to develop NMO but are not developing it because of ongoing immunosuppressants for the primary non-NMO immunological condition. Whether it is meaningful to screen patients with connective tissue disorder for AQP4 antibodies as part of the

screening strategy is debatable. The morbidity associated with NMO is so high this might be a strategy that might be employed in the future.

Optic neuritis or transverse myelitis patients who are seropositive for NMO-IgG and also having Systemic sclerosis (SS)/Systemic lupus erythematosis or non-organ-specific autoantibodies is thought to be an indication of coexisting NMO rather than a vasculopathic or other complication of SS/SLE(16, 67). I found one patient with SLE or SS.

4.4. 9. CSF oligoclonal bands:

CSF OCB was absent in 85% of patients with NMO in line with other studies. CSF often showed acute changes of pleocytosis and raised protein often with eosinophilia but spinal fluids were not done acutely in many patients and even if done it were often difficult to obtain the dates of the spinal fluid studies in relation to the clinical event. These markers are technique and technician dependent which vary between the laboratories. Iso-electric focusing which has a higher sensitivity and specificity may not be used as standard in the detection of oligoclonal bands with many labs still using gel electrophoresis.

4.4.10 Opticospinal demyelination- Unclassified:

At the median of 3.2 years (0-5.5) of follow up , 27 patients remained as unclassifiable opticospinal demyelination. We were unable to categorise them into either typical relapsing remitting MS (i.e. with oligoclonal bands and MRI brain abnormalities) or NMO. This group has several peculiarities. Their relapses are almost always confined to optic nerve and the spinal cord. The spinal cord lesion length is always less than 3 cm. CSF oligoclonal bands were absent in 18/27 (67%) and MRI of the brain did not have the widespread lesions typical of multiple sclerosis. Though "lumpers" might class them as multiple sclerosis, and others may call it NMO with short cord lesions and negative NMO antibodies, it is possible that this group too is a separate entity or

subtype of MS. The distinction is clinically important as treating NMO with beta-intererons as in MS, can exacaerbate it(68). I believe that these groups need to be followed up for a longer term with repeat MRI and reanalysis of sera to look for possible new markers.

4.4.11 Other limitations of the study

Radiological data was collected where possible but not analysed. There are several reasons for this: The number of scans available for review was few. It was impossible to transfer all scans across to the Walton Centre to be reviewed by a neuroradiologist as these were largely hard copies. Many patients were diagnosed in the pre-MRI era. Many centres had destroyed MRI scans due to storage difficulties. Longitudinally extensive myelitis which is typical NMO or NMOSD is seen only in scans which are done soon after relapse and many scans were not done acutely. The spinal cord in resolved lesions can often be normal with the exception of atrophy or a syrinx. Gadolinium was not given routinely. I therefore did not proceed to analyse this data or incorporate them into this work as it would not have made any meaningful difference to what is already known.

Using the BNSU as the central referral mechanism has advantages and limitations. The advantages include a centrally held database of all Neurologists and uninterrupted monthly reminders to Consultants by a recognised and respected central organisation. However the referral process depends on the Consultants being members of the Association of British Neurologists, and more importantly the Consultant's willingness and ability to identify and refer patients on to the BNSU.

Apart from this busy multiple sclerosis clinics (where NMO patients are usually followed up) review appointments are usually only made once in six months or a year and there is no certainty that an individual consultant /registrar would recognise and re classify as NMO, a patient in remission, who has long before been diagnosed as MS.

Conusltants also hesitate to refer as this creates additional work like to filling in forms and making arrangements for my visit to the Hospital. There were occasional instances where neurologists referred patients but did not proceed to the next level of organising notes and scans due to the work involved to them or their secretaries.

Ideally all of the neurologists in the Country would be enlisted to participate in such a study, would search for the condition in their medical records of their respective hospitals and patients would be seen at each hospital using standard diagnostic criteria and the data transferred to the chief investigator. These patients could then be followed up. Better still would be a survey of all GP Practices within the UK. such as the study as done in Cuba, that would capture most patients(4). The time, effort and resources required for such a project were outside the scope of this study.

Chapter 5:

Treatment of Neuromyelitis Optica with Rituximab

5.1 Introduction:

There are no randomised trial recommendations to prevent relapses in NMO. Studies are based on small case series. Immunosuppressant medications including azathioprine(41), cyclophosphamide, mitoxantrone(44), mycophenolate mofetil(45) are used. Interferon beta is reported to be less effective than immunosuppressive therapy(69) or deleterious(48). Open label use of rituximab (Rituxan, Biogen-IDEC, Genentech, San Francisco, CA), a monoclonal antibody against CD20 B-cells has been reported in NMO (42, 70). Given the lack of other treatments proven to be effective, this report led to wide use of rituximab for NMO, even as a first line treatment. However there is a clear need for further information about the role of Rituximab in NMO. I therefore conducted a retrospective analysis of the use of rituximab in patients with NMO under the guidance of Professor Weinshenker and Dr Cree

5.2 Methods:

Investigators from twenty centres in the USA and UK who attended an exploratory meeting in San Fransicso, USA about a potential clinical trial of a new humanized monoclonal antibody with similar specificity for CD20 protein as rituximab were approached to participate in this study. Seven centres responded to the request and contributed all the patients to whom rituximab was administered for treatment of NMO by the recollection of the site investigators [UCSF, San Francisco, CA, USA (n=7);Stony Brook Hospital , NY (n=6);Mayo Clinic Rochester, MN (n=5);, Mayo Clinic Scottsdale AZ (n=2); The Walton Center, Liverpool, United Kingdom (n=2);, Mellen Center, Cleveland Clinic Cleveland, OH (n=2); Mount Sinai Hospital, NY (n=1)]. IRB approval was obtained at each centre and consents were obtained from patients or next of kin. All patients with relapsing NMO or longitudinally extensive transverse myelitis (LETM)(30) who were treated with at least one dose of rituximab and who had at least six months of follow up were included.

Patients who did not meet the above criteria were excluded. I analysed completed case report forms whilst at the Mayo Clinic, Rochester, Minnesota. All patients reported to the analysis team by the treating hospitals were found to be eligible and were included. Statistical analysis was performed using JMP 6.0 (SAS, Cary NC).

5.3 Results:

5.3.1 Patient characteristics

Twenty five patients were reported and all satisfied inclusion and exclusion criteria. There were three men and twenty two women. The median (range) age of the patients was 38 (7-65). Two children were included in whom rituximab was begun at age seven (patient 8, Table 1) and 14 (patient 11). Twenty three patients had NMO and two had relapsing LETM. The median (range) interval from onset of NMO to treatment with rituximab was 4.5 (0.8 -17) years. The clinical and demographic profile is outlined in table 1. NMO IgG was positive in 14 of 20 patients. Seven of eight patients from the initial study are also included(42). One patient from the initial study was lost to follow-up.

Rituximab was initiated in 23 patients due to failure of other medications (Table 1). In 19 patients more than one drug was used (Table5.1). In two patients, rituximab was used as the first drug

Patient No	Gender	Diagnosis	Age at initiation of rituximab treatment(years)	Duration of Disease when RTX initiated (years)	NMO IgG status	LETM on MRI	Drugs used Prior to Rituximab
1	F	NMO	49	4.84	-	+	GA (7)
2	M	NMO	28	5.25	+	+	IFN(24), AZ(28), IVIG(23)
3	F	NMO	19	4.62	+	+	AZ(9) IFN(7)
4	F	NMO	43	2.09	-	+	None
5	F	NMO	43	17.22	Not Done	+	AZ(U)P(U) MITOX(2) CYCL(U) MMF(U)
6	M	NMO	22	15.79	+	+	AZ(U) P(U) MET(U)
7	F	NMO	40	6.77	Not Done	+	GA (9) AZ(13) IFN(3) MITOX(2) AZ(20) P(20)
8	F	NMO	7	4.17	+	-	P(3)
9	F	NMO	21	7.92	+	+	IFN(6) AZ(27) CYCL(1) MTOX(2)IFN
10	F	NMO	53	3.68	+	+	MITOX(5) AZ(6)
11	F	NMO	14	7.25	-	U	P(7)IVIG(U)
12	F	NMO	50	0.83	Not Done	+	U
13	F	NMO	33	2.89	+	+	IFN(U), IVIG(U)
14	F	NMO	28	6.08	Not Done	+	IFN(60) AZA(72) P(24) IVIG(15)
15	F	NMO	18	8.17	+	+	IFN(102) MITOX(3) IVIG(4)
16	F	NMO	19	6.32	+	+	IFN(12) GA(3) IF(45) IVIG(7) MITOX(3)
17	F	NMO	22	7	+	+	IFN (12) AZA (14) MITOX (22) AZA(4)
18	F	NMO	52	4.25	-	+	IFN(26)
19	F	NMO	54	1.17	+	+	AZA(5) P(5)
20	F	Relapsing Myelitis	43	4.13	+	+	Hydroxychloroquine (1) AZA(53) P(12)
21	F	Relapsing Myelitis	43	2.62	+	+	CYCL(22)
22	F	NMO	35	3.63	-	+	GA(24)
23	F	NMO	47	3.1	+	+	P(3) AZA(6)
24	M	NMO	62	2.88	Not Done	+	IFN(4) AZA(2)
25	F	NMO	24	4.93	-	+	AZA(12) P(12) IFN(33) IVIG(1)

Legend to table

5.1Table 1: **Clinical profile of rituximab-treated patients** NMO—neuromyelitis optica, GA–glatiramer acetate, IFN–interferon beta, AZA-azathioprine, IVIG - Intravenous immunoglobulins, P-prednisone, MITOX- mitoxantrone, CYCL – cyclophosphamide, MMF-Mycophenolate, MET-methotrexate, U unknown, LETM- Longitudinally extensive transverse myelitis

5.3.2 Treatment with rituximab

Two dosing regimens of rituximab were used as the initial treatment. These were based on use in rheumatology(71) haematology(72) and the previous reported series of 8 patients(42) and were guided by local practice. Regimen 1) 375mg/m^2 of rituximab was infused four times with a one week interval between infusions (n=18)(72); 2) 1000mg of rituximab was infused two times with a two week interval between the infusions (n=4)(71). Information regarding dosing regimen was unavailable for three patients. Seventeen patients received further rituximab treatments: Eight had further doses of 375 mg/m^2; seven had 1000mg rituximab two weeks apart; data regarding subsequent dosing regimen were unavailable for two patients. Other immunotherapy was used in five patients along with rituximab: azathioprine + prednisone (n=1), prednisone (n=3), interferon beta (n=1).

The median (range; mean) interval between the last relapse and start of treatment was 1 month (0-7; 1.5). 20 of the 25 patients received treatment within 2 months of the last relapse. The median (range) interval between rituximab treatment courses was 8 (4-26) months. Subsequent treatments were either pre-planned at 6-12 month intervals or were administered after relapse or when CD19 cells were again detectable. CD19 counts were not routinely monitored in all patients and no threshold value was utilized to determine frequency or timing of re-treatment.

5.3.4 Follow up

The follow up interval after initial rituximab treatment was 19 (6-40) months [median (range)]. Eighteen patients planned to continue treatment with rituximab at last follow-up and 15 had received rituximab in the last six months of follow-up.

Seven patients discontinued treatment. The reasons for discontinuation were death (n=2; patients 5 and 10), relapses (n=2; patient 18 and 22), pregnancy (n=1; patient 14) and other (n=2; patient 13 and 20).The details of these seven patients are given below.

Three patients started other remission-inducing treatments (patients 18, 20, and 22). Patient 18 was initiated on maintenance plasma exchange every six weeks, pulsed intravenous steroids and mycophenolate mofetil. Patient 22 was placed on cyclophosphamide after the third relapse. Patient 20 who was on azathioprine throughout, was averse to parenteral administration of drugs, and wanted to retry azathioprine. So after two minor relapses the dose of azathioprine was increased and she remains relapse free. One patient planned pregnancy (patient 14). One (patient 13) discontinued rituximab and was not on any new treatment despite a minor relapse (figure 1). However, after completion of this analysis she was readmitted with a severe spinal cord relapse at 2 years from last infusion of rituximab (not shown in fig 1) and has now resumed rituximab; this relapse was not included in the analysis of relapse rate.

5.3.5 Efficacy : *Relapse rates*: Relapses before and after treatments are represented in figure 5.1. All relapses after onset of rituximab were considered. However if new treatments were introduced, only relapses until the start date of the new treatment were included (patients 18, 20, 22). Relapses in patients who stopped rituximab but were not on any other treatments were included. If all patients were included (n=25) the pre-treatment annualized relapse rate was 1.7 (0.5-5; 2.7) and the post-treatment was 0 (0-3.2; 0.6) [Median (range; mean)] ($p < 0.0001$, Wilcoxon signed rank test) at a median follow up of 19 months.

If the two patients who died (patients 5 and 10) were excluded from relapse analysis (n=23) the pre-treatment annualized relapse rates was 1.7 (0.56-4.9; 2) and the post-treatment was 0 (0-3.2; 0.63) ($p < 0.0001$).

If the five patients who were on any additional immunological treatment (7, 11, 15, 19, 20) and the two who died were excluded, the pre-treatment relapse rate was 1.7(0.7-4.9; 2.12) and the post treatment relapse rate 0(0-2.9; 0.5) at a median follow up of 18 months

in the remaining 18 patients. If the patients who were followed less than one year were also excluded (1,2,3,4) along with those on any additional immunological treatment (n=5) or who died (n=2), the pre-treatment relapse rates were 1.5(0.7-4.9; 2.2) and the post treatment relapse rates 0(0-2.9; 0.46) respectively at a median follow up of 22 months in the remaining 14 patients.

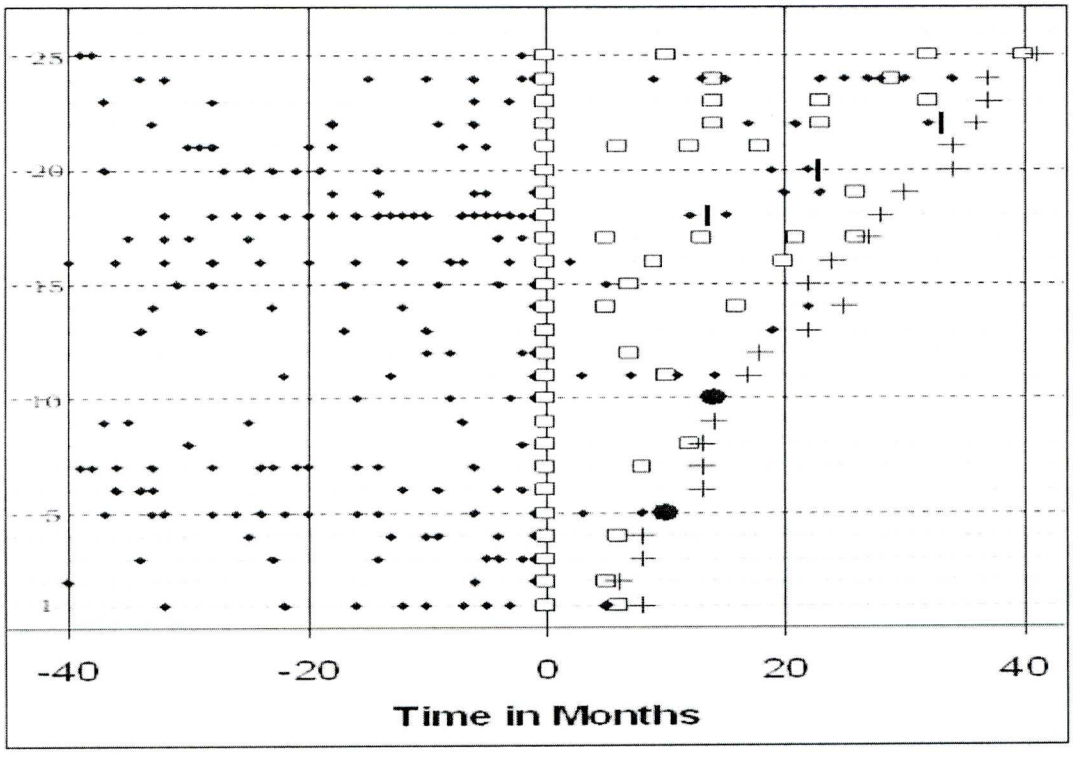


Fig.1. **Pre and post rituximab relapses.** Each interrupted line on the y axis represents a patient. The x axis indicates the 20 months pre and post rituximab treatment. The open white boxes (□) indicate RTX treatment. The black diamonds (♦) indicate relapses. The plus (+) signs indicate last follow up and the black solid circles (●) indicate deaths. The vertical lines (|) indicate start of new treatments.

5.3.6 Efficacy*: Disability*: Two patients died (Patient 5 and 10). The median (range; mean) EDSS at start of treatment with rituximab was 7(3-9.5; 6.8) and that at last follow up at a median of 19 months was 5 (3-10; 5.5) n=25

EDSS scores of 20 patients stabilized (n=9) or improved (n=11). In five patients (patient 3, 5, 10 13, and 20) EDSS scores worsened.

The number of patients in the two treatment regimes was different (18 treated with 375mg/m^2 and four with 1000 mg); data was unavailable about the specific treatment regimen for the remainder. Subsequent treatments were variable, making comparison between dosing regimens difficult. Hence analysis was not attempted.

5. 3.7 Adverse events observed during treatment and follow up

Infusion-related transient side effects occurred in seven of 25 (28%) patients and were not dose-limiting. New or reactivated infections developed in five of 25 (20%) patients and included: herpes simplex (cold sore) and positive PPD (n=1) herpes zoster (n=1), recurrent *Clostridium difficile* colitis (n=1), cutaneous fungal infection (n=1), urinary tract-related septicaemia and death (n=1).Worsening of pre-existing seborrheic dermatitis occurred in one patient.

5.3. 8 Deaths: Patient five developed recurrent *Clostridium difficile* colitis after her first rituximab infusion followed by urinary tract infection. She died nine months after the last dose following a severe brainstem relapse accompanied by a brainstem lesion extending into the hypothalamus and thalamus detected on MRI. Clinical manifestations were lethargy, obtundation, electrolyte imbalance and hypothermia. CD19 cells were not detectable two months before death and seven months after last infusion.

Patient 10 died six months after the last dose of rituximab. She was obtunded and was suspected of being septic. An autopsy restricted to brain and spinal cord showed confluent demyelination in the cord from lumbar to cervical cord with focal necrosis and cavitation, perivascular lymphoid infiltrate and macrophage infiltrates. Both optic nerves

were atrophic and had lymphocyte and macrophage infiltrates. The brain did not show any pathology. CD19 cells were undetectable five months after last infusion and one month before death. Her total lymphocyte count was $0.9x10^9$ just before death (normal 0.9-2.9 $X10^9/L$) compared to $2.73x10^9$ before starting rituximab; she had low IgA, IgG, IgM levels one month prior to death. Prior to initiation of rituximab she was treated with mitoxantrone.

5.4 Discussion

NMO is a relapsing disorder with rapid accrual of attack-related disability and a high early mortality rate(11). Controlled trials of treatments to prevent relapses are unavailable and treatment is based on case series and expert opinion. Though two cases were reported to enter remission with use of glatiramer acetate(73, 74) immunomodulatory medications (beta interferons or glatiramer acetate) do not appear to be beneficial in larger case series(48, 69). Immunosuppressive drugs are the mainstay of treatment in NMO. Azathioprine(41) is the most widely used medication. Cyclophosphamide, mitoxantrone(44), cyclosporine, methotrexate (75),and mycophenolate mofetil (45) have been used(76). However, patients commonly relapse on these treatments and relapses with brainstem or cervical cord involvement are a frequent cause of death in NMO(11).

This retrospective, multicenter case series evaluated the use of rituximab in NMO largely refractory to the other drugs. Relapse rates improved and disability stabilized or improved in 20/25 (80%) patients similar to the previous findings in a much smaller series (42).

Though the infections cannot be definitively classified as opportunistic, death of one patient due to sepsis and the occurrence of infections in others are of concern. Patient 10 died following a presumed UTI and had reduced lymphocyte counts and immunoglobulin

levels. It is possible that treatment with rituximab, and/or prior treatment with mitoxantrone, contributed to the patient's infections.

No attempts to identify factors predictive of response to rituximab was made. The small size, retrospective acquisition of data and positive treatment response in 80% patients precludes such an analysis.

It is unclear whether rituximab should be the first line treatment for NMO. Comparative studies between the immunosuppressive treatments used in NMO have not been undertaken. The patients in this series are a selected population of treatment-refractory NMO. Perhaps the majority of treatment naïve patients may need less expensive and widely available immunosuppressive drugs. Also even in this small group, there are apparent rituximab treatment failures demonstrating that, it may not effective in all patients. A recent case report on 2 patients with variable response to treatment with rituximab highlights this(70)

Safety concerns regarding rituximab persist. The relative risk of infections with rituximab versus other immunosuppressive treatments in NMO is unknown. Recent reports of progressive multifocal leukoencephalopathy (PML) in two patients with systemic lupus erythematosus(SLE), one patient with systemic vasculitis and 23 patients with lymphoma treated with rituximab are of concern(77). However these patients received treatment with other immunosuppressive medications, either sequentially or in combination with rituximab. Lymphomas and SLE are thought to predispose to PML, irrespective of treatment. PML has also been associated with azathioprine(78, 79), cyclosporine(80, 81) and cyclophosphamide(82).

Rituximab treatment is substantially much more expensive(83) than generic immunosuppressive drugs such as azathioprine. However, this may be offset against the cost of hospitalizations for relapses and plasma exchanges if rituximab is more efficacious.

5. 5 Limitations:

This study is limited by the retrospective nature of this multicenter case series. The treatment regimens differed although the total dose administered to each patient was comparable. The intervals between courses of treatment were variable. It is possible that 'regression to the mean' contributed to the decline in relapse rates. The wash-out period between rituximab and previous drugs was often insufficient. A combination of drugs was administered to five patients. CD19 B-lymphocyte counts were not measured to assess efficacy of treatment and timing of retreatment. The pretreatment EDSS may have been determined immediately post-relapse, while the last available EDSS may have been determined during a period of stability, thus showing improvement attributable to recovery from an attack.

Despite these limitations I feel that this study is valuable. Much has been learned on pathogenesis and course of NMO in the recent years. But data on treatment in NMO are sparse, and there are no data from controlled trials. This is a large series of a single drug treatment, particularly of the subgroup refractory to conventional treatment which has a high mortality. Controlled trials are difficult to organize due a variety of reasons due to the rarity of the disease, need for early treatment, high morbidity from relapses but it should become a priority to physicians caring for people with NMO. Until then studies such as this provide 'some evidence' to guide the choice of treatment for this potentially life threatening disease.

Chapter 6

Treatment of Neuromyelitis Optica with Mycophenolate Mofetil

6.1 Introduction

No randomised controlled trials have been conducted in NMO and treatment is empiric, based on small case series. The mainstay of treatment for a majority of patients is prednisone alone or in combination with Azathioprine. Its use is largely based on a series of seven NMO patients who were treated with long-term prednisone and azathioprine and were followed every 2 months for at least 18 months. Their EDSS score improved significantly and no relapses occurred for more than 18 months(41). A similar small case series on 5 patients on mitoxantrone over 2 years also showed improvement (44). 2 patients each had a relapse once within the initial 5 months of treatment. 1 patient had a reversible decrease in cardiac ejection fraction.

Rituximab a monoclonal antibody against $CD20^{+}$ B cells(43)has been used in NMO. Following an initial report on 8 patients, I conducted a retrospective multicentre experience on twenty five patients showed that the drug seemed effective in reducing relapse rates and improving or stabilising disability in 80% of treated patients(42, 84). However 28 per cent of patients had infusion related adverse events and 20 percent had infections that could possibly be reactivated due to immunosuppression. Two patients died, one likely due to septicaemia. Rituximab, therefore, was potentially beneficial but seemed associated with the risk of infections. But even in this small series there were treatment refractory patients. It also requires intravenous infusion, which may necessitate admission. These factors and the risks of significant infections from immunosuppression may limit its use, especially as a first-line agent in the treatment of NMO spectrum disorders.

Mycophenolate Mofetil (MMF)(Cellcept®, F.Hoffmann-La Roche, Basel, Switzerland) is 2- morpholinoethyl ester of mycophenolic acid and a reversible inhibitor of inosine monophosphate dehydrogenase involved in the de novo (but not salvage) pathway for

guanosine nucleotide synthesis, on which the T and B Lymphocytes are exclusively dependent for proliferation(85). It also exerts an inhibitory effect on antibody synthesis. It is routinely used in cardiac and renal transplants and is being increasingly used as a treatment option in a variety of other immunological conditions including lupus induced and other immune nephropathies, autoimmune hepatitis, psoriasis, blistering dermopathies, and vasculitides. Neurologists are familiar with the drug due to its use in myasthenia gravis(86-89).There are reports of its use in multifocal motor neuropathy(90), inflammatory myopathies(91), CIDP(92), autonomic ganglionopathy(93) vasculitic neuropathies (94)and multiple sclerosis(95-97). It is considered to have fewer side effects than other immunomodulators and is given orally. All of these factors may have favoured its off label use in NMO, insufficient published evidence exists for its benefit in NMO.

Only one case of NMO treated with MMF has been reported(45). A 9 year old girl with NMO had 5 relapses over 2 year period despite azathioprine. Steroids caused a vertebral fracture. MMF introduced 16 months after onset of NMO was able to sustain a remission at 2 years(45). The dose, duration, and efficacy of the drug for NMO remain uncertain.
I therefore did another study under the guidance of Dr Sean Pittock to assess the efficacy of MMF.

6. 2 Methods

A retrospective chart review of ***all* Mayo Clinic patients** with NMO (as per 2006 diagnostic criteria) or a NMO spectrum disorder (NMO-IgG seropositive patients with optic neuritis or longitudinally extensive transverse myelitis) treated with MMF from June1999 until June 2006 was performed. Patients were identified by searching the centralised medical records of all the 3 Mayo Clinics sites [Rochester (MN), Scottsdale (AZ) and Jacksonville (FL)] using the search terms "Neuromyelitis optica" or "Devic's disease" or "optic neuritis" or "myelitis" and "mycophenolate" or "cellcept."

Local institutional review board approval was obtained and informed consent was obtained from patients or the next of kin. Telephone follow up was performed in June 2007 and more recently in August 2008(49). Data was analysed using JMP, Version 6.0 (SAS, Cary, North Carolina). Wilcoxon signed-rank test was used to compare pre and post treatment relapse rates and EDSS. Relapses and disability were assessed by chart review and telephone interview. A relapse was defined as objective worsening of neurologic function lasting for more than 24 hours. Pseudo-exacerbations (temporary increase in symptoms) brought on by heat, exertion or fever were not considered attacks.

6.3 Results

6.3.1 Patient Characteristics

Twenty-four patients were identified. There were 19 women and 5 men. The median age of the patients at onset of treatment with MMF was 56 (range 34-77) years. The median duration of NMO to onset of treatment with MMF was 4.2 years (range 0.1-39). The diagnosis was NMO in 15 [(63%); 13 of 14 were NMO-IgG seropositive, and all fulfilled 2006 NMO diagnostic criteria]; relapsing LETM in 7(29%); relapsing optic neuritis in 1(4%) and a single episode of LETM in 1 (4%). The patients with LETM and optic neuritis were all NMO IgG seropositive.

6.3.2 Treatment with Mycophenolate

Seven (29%) patients were treatment naïve. The remaining 17 (71%) were tried on other immunosuppressive (n= 6), immunomodulatory (n=2) or a combination (n=9) therapy, Twelve (50%) received Azathioprine (Table 1). Reasons for switching to MMF were identified in all and included medication side effects in 7(29%), continued relapses in 8 (33%), contraindication to azathioprine due to low thiopurine methyltransferase (TPMT)

levels in 2 (8%). The median dose of MMF used was 2000 mg/day (range 750-3000). The clinical and demographic profiles of the patients are summarized in the table.

6.3.3 Follow Up

After identification of the initial cohort in June 2007, telephone follow up and chart review was again obtained, for 20 patients in late 2008, at a median of 27 months after starting treatment (18-89). For 4 patients who were not contactable (one died) by telephone recently, chart review provided data up to a median 46 months (21-54). The median follow up of all patients (irrespective of whether they stayed on treatment) was 28 months (range18-89).

The median duration of treatment on MMF was also 27.4 months (range 1-89). At last review 19 (79%) patients continued on treatment with MMF with a median duration of 29.4 months (range 20-89). Five (21%) patients discontinued the drug after a median duration of 16 months (1-54). The reasons for discontinuation were death in one (patient 21) , relapses in two (patient 3 switched to rituximab at 3 months and patient 14 to azathioprine at 25 months) and side effects in one (patient 2, low WBC counts, who switched to azathioprine at 1 month). Patient 1 had neither relapses nor side effects but chose rituximab at 1 month.

6.3.4 Treatment Efficacy : Relapse Rates

Figure 6.1 shows the relapses before and after treatment. All relapses after initiation of MMF until its discontinuation or until the last date of follow up was included in the analysis. Nine patients were on additional treatments [steroids (n= 8) and IV immunoglobulins (n=1)] for variable periods after starting MMF (table 1).

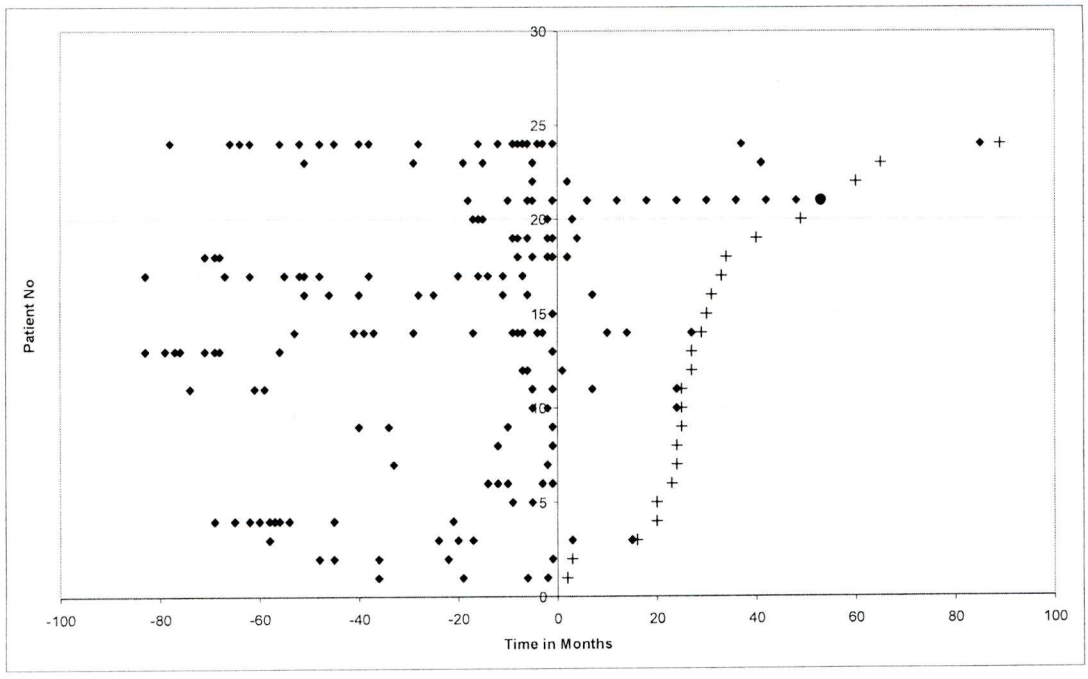


Fig.6.1. **Pre and post mycophenolate relapses**. Each interrupted line on the y axis represents a patient. The x axis indicates the 100 months pre and post rituximab treatment, 0 being the start date of treatment. The plus (+) signs indicate last follow up or date of discontinuation of treatment ;(•) indicate deaths. The relapses of patient 21 are distributed evenly over his MMF treatment duration due to incomplete data.

Entire Cohort: The median treatment duration for all 24 patients was 27.4 months (range 1-89), the median annualised post treatment relapse rate was 0.09 (range 0-1.56) and the pre treatment rate was 1.28 (range 0.23-11.78, $P<0.0001$, Wilcoxon signed-rank test). Nineteen of the 24 patients (79%) had an improvement in relapse rates. As analyses of the total group were confounded by concomitant treatments, short duration of treatments and death, I performed subgroup analyses.

Subgroup analysis 1: Duration of therapy

Two of the 24 patients were on MMF for a very short duration (patients 1 and 2 for one month each) and discontinued the drug early due to side effects. If these patients were

excluded from the analysis, the remaining 22 patients had median treatment duration of 28 months (16-89). The median post treatment annualised relapse rate on treatment for these 22 patients was 0.19 (range 0-1.56) versus the pre treatment rate of 1.37 (range, 0.23-11.78, P <0.0001). 17/22 (77%) patients had an improvement in relapse rates.

Subgroup analysis 2: Death and Duration of therapy

If I exclude the patient who died (patient 21) along with those with short follow ups (patient 1 and 2) the median duration on treatment for the 21 patients was 27.4 months (range, 16-89). The median post treatment annualised relapse rate on treatment for this subset was 0.18 (range, 0-1.5) and the pre treatment rate was 1.15 (range, 0.23-11.78, P <0.0001).

Subgroup analysis 3: Death, Duration of Therapy and Concomitant therapies

If patients who were on any additional treatment (3,5,6,9,12,13,15,21 and 22) and those on treatment for less than a month (patients 1 and 2) and the patient 21 who died were excluded, the median duration of treatment in months was 31 (range, 21-89) for the remaining 12 patients. The median post treatment annualised relapse rate on treatment for this subset was 0.24 (range 0-1.22) and the pre treatment rate was 1.15(range 0.23-7.6, P <0.001).

6.3.5 Treatment Efficacy: Disability

The median Expanded Disability Status Scale (EDSS) score at the start of treatment with MMF (n=24) was 6 (range, 0-8) and at last follow-up at a median of 28 months was 5.5 (range, 0-10) (*P*=0.17). Excluding the 2 patients who were on very short period of treatment (n=22), did not alter the median scores.

The EDSS scores were unchanged in 15 and improved in 7 (22/24, 91%). The median reduction in EDSS was 1 point (0-5 - 2.5). Four of these patients stopped using their cane.

EDSS worsened in 2 patients (patient 3 who worsened from EDSS 6 to 8 and patient 21 who died after being bed bound for 54 months).

6.3.6 Adverse Events Observed During Treatment And Follow-Up

One patient (21) died. This was a 45 year old Hispanic man who presented with optic neuritis and myelitis in 1999 and had a further 3 relapses in the same year. He was initiated on MMF and prednisone in 2000, after developing liver dysfunction with azathioprine. No side effects were noted in the initial year. He was lost to follow up. Recent telephone discussions with family indicate that he continued to relapse once every six months while on MMF (exact details not available) and died 54 months after onset of treatment with MMF. The death certificate documents the cause of death as 'cardiopulmonary failure; respiratory drive failure and Devic's disease'. The relapses indicated in the figure 1 are evenly distributed over the period of follow up.

Six patients (25%) reported side effects: headache (n=1), constipation (n=1), easy bruisability (n=1), anxiety (n=1) hair loss (n=1), diarrhea and abdominal pain (n=1, dose limiting,) and low WBC counts (n=1, needing change of drug)

6.4 Discussion

NMO is considered to be a rapidly disabling disorder with attack related early accumulation of disability. Preventing attacks by immunosuppressive drugs is the mainstay of preventing disability(98). Azathioprine(41), corticosteroids(99), mitoxantrone(44) and more recently rituximab(42, 43) have been found to be useful in small case series. Rituximab seemed to be potent in reducing relapse rates in these retrospective series. In one series, 23 of 25 patients were refractory to other treatments

(compared to 17 of the 24 in this cohort) including 1 patient who was on MMF. Only 2 patients were treatment naïve (compared to 7 in the present study). However, even in the 25 patients treated with ritiximab, there were treatment refractory patients (2 ; one each switched to azathioprine and MMF), side effects and 2 deaths. No patient was tried on rituximab prior to MMF in the present study.

The wide use of MMF in rheumatology and transplant medicine and myasthenia gravis has prompted its use in NMO and this retrospective study is intended to summarise the treatment experience at the Mayo Clinic. I found that the relapse rates were improved in 19/24 (79%) patients and disability stabilised or improved in 22/24 patients (91%). Identifying reliable predictors of response was not attempted as the good response to treatment in majority; varying doses and additional treatment in 9 patients are strong confounders. The side effects observed in this study were dose limiting in one patient and necessitated change to azathioprine in another.

Despite the apparent benefit, serious safety concerns exist with mycophenolate.
Progressive multifocal leukoencephalopathy (PML) has been reported in kidney, heart and lung, transplant patients and in systemic lupus erythematosis (SLE)when MMF was used in conjunction or after the use of other immunosuppressants (100). A retrospective cohort study of 32,757 renal transplant recipients using the United States Renal Data Systemkidney transplant files identified 9 cases. Based on this the incidence density of PML in MMF users was 14.4 cases/100,000 person-years at risk versus 0 for non-MMF users. However as 75% of patients in the cohort were on MMF no statistically significant association was found. No cases were seen in patients on MMF monotherapy(101).
Though an increased risk of lymphoma was initially reported in patients who underwent transplants and occasionally in autoimmune disorders (102-105), an international

prospective registry of 6751 patients receiving MMF and an equal number of matched controls receiving non mycophenolate-based immunosuppression, did not find this association, at least in renal transplant patients with lupus nephritis(106).

There are also concerns regarding efficacy of mycophenolate. Though the drug had ample anecdotal evidence supporting its use(89), the two large recently concluded randomised controlled trials in myasthenia gravis showed no benefit (87, 88, 107). There are also reports on the lack of advantage over azathioprine in recipients of cadaver kidney-transplants in preventing acute rejections (108). MMF is also much more expensive than azathioprine, but cheaper than rituximab. I used an online drug store to compare drug prices (109). This I felt might be a better option than prices from hospital pharmacies, where discounts might apply and costs may vary across the country. The estimated drug cost for azathioprine, MMF and rituximab for one year were $846.8 (150 mg /day), $11373.4 (2000mg/day) and $23,287.6 (four 1000 mg infusions/year) respectively. Additional expenses related to drug infusions (eg; day admission) for rituximab and regular laboratory based monitoring (liver function tests and complete blood counts) for azathioprine and MMF would also factor in the overall cost.

6.5 Limitations of the study.

The predominantly retrospective (and 14 month prospective) nature of the evaluation, the small cohort of patients and use of additional treatments make definitive statements on the effectiveness of the drug perilous. The reduction in the relapse rates could be a regression to the mean phenomenon(110). The pre-treatment EDSS could be at a time of relapse while the post treatment scores could be during a period of stability. It is also possible that the observed efficacy of MMF could be the continued benefit from the drug

preceding it. The loss of follow up and subsequent death of one patient due to unknown causes also adds to some uncertainty.

There is no consensus amongst neurologists on the drug of first choice for relapse prevention in NMO. There have been no controlled trials in NMO (let alone comparative trials) and azathioprine with or without oral prednisone, rituximab, MMF and other immunosuppressants all seem effective; therefore, side-effects and cost along with the urgency in rendering the patient immunosuppressed influence this decision. It is uncertain if the benefits seen in this study will be borne out in controlled clinical trials. But this case series might provide some justification to the use of the drug in patients experiencing life-threatening relapses and for organising a multicentre trial comparing the currently used drugs.

Patient No	Gender	Diagnosis	Disease duration at first Mycophenolate treatment (Years)	NMO IgG status	LETM on MRI	Drugs used Prior to Mycophenolate	Concomitant immunotherapies
1	M	Relapsing myelitis	3	+	+		
2	M	NMO	4.08	+	+	Azathioprine	
3	F	NMO	6.83	+	+	Interferons	Oral prednisone
4	F	NMO	5.89	+	+	Azathioprine, Inteferons, Prednisone	
5	F	Relapsing myelitis	0.83	+	+	Azathioprine	Prednisone on alternate days
6	F	NMO	1.17	+	+	Glatramer acetate	Pulsed intravenous methylprednisone monthly
7	F	NMO	1	U	+		
8	M	Relapsing myelitis	2.75	+	+		
9	F	NMO	12.5	+	+	Azathioprine, Prednisone, Intravenous immunoglobulins	Intravenous immunoglobulin monthly
10	F	Relapsing myelitis	1.25	+	+		
11	F	Relapsing myelitis	6.25	+	+	Interferon , Prednisone	
12	F	Relapsing optic neuritis	10.83	+	-		Oral prednisone
13	F	NMO	26.33	+	+	Azathioprine, Interferon, Glatiramer acetate, Methotrexate	Oral methyl prednisone 1g/month
14	F	NMO	18.16	+	+	Prednisone, Glatiramer acetate, Mitoxantrone, Cyclophosphamide, Interferon	
15	F	Single episode of myelitis	0.08	+	+		Oral prednisone 5mg daily
16	F	NMO	13.01	+	+	Azathioprine, Intravenous methylprednisone, Interferon, Mitoxantrone, Methotrexate	
17	F	NMO	25.83	+	+	Glatiramer acetate, Azathioprine, Interferons, Prednisone	
18	F	NMO	38.75	+	+	Azathioprine, Interferon, Intravenous immunoglobulins	
19	F	NMO	0.66	+	+		
20	F	Relapsing myelitis	1.5	+	+	Cyclophosphamide	
21	M	NMO	1.42	+	+	Azathioprine, Prednisone	Prednisone, Intravenous methylprednisone

22	F	Relapsing myelitis	0.25	+	+	Azathioprine	Pulsed Intravenous methylprednisone
23	F	NMO	4.33	+	-	Azathioprine, Prednisone, Cyclophosphamide	
24	M	NMO	6.5	+	+	Azathioprine, Interferon	

Legend to table 6.1

Table 1: **Clinical profile of mycophenolate treated patients**

NMO—neuromyelitis optica, U- unknown ; + present ; - absent; F- female; M- male

Chapter 7.

Discussion and Conclusions

Since this study began major advances have occurred in NMO by various groups across the world. These were spurred on by the discovery of the antibody marker and its antigen- aquaporin-4(32, 111).We now have a better understanding of the partners and mechanisms of antiaquaporin-4 antibody

AQP-4 antibodies are produced by B Cells in peripheral circulation and access its antigenic target the water channel AQP4 on astrocyte membranes. Regions with high expression of AQP-4, like the foot processes of astrocytes abutting the capillary walls in the blood brain barrier, optic nerve head, spinal cord and those regions where no blood brain barrier exists -circumventricular organs – seem more susceptible to such damage. After crossing the blood brain barrier, binding occurs only to macromolecular aggregates of AQP4 (orthogonal array particles, OAP). Only the M23 isoform of AQP4 (and not M1) form such OAPS (112). AQP4 and the sodium dependent excitatory amino acid transporter 2 (EAAT2) co-exist as a complex on the plasma membrane. EAAT2 is crucial to the re uptake of glutamate(34). The binding of AQP4-Ab to AQP-4 on astrocytes leads to the AQP4 being internalised by the cell [into early endosome antigen 1 (EEA1) containing early endosomal vesicles with probable subsequent degradation (113-115)] along with EAAT2 resulting in impaired glutamate uptake leading to excessive glutamate outside the cell. The resulting over stimulation of glutamate receptors in neurons and oligodendrocytes could contribute indirectly to the pathobiology of NMO. This in turn leads to injury to neurones and oligodendrocytes in the vicinity(34). EAAT2 accounts for > 90% of glutamate uptake in the CNS and is critical for clearing glutamate from excitatory synapses, and is expressed selectively in astrocytes. AQP4 and EAAT2 exist in astrocytic membranes as a macromolecular complex. Because astrocytes are

relatively tolerant of increased glutamate concentrations disruption of glutamate homeostasis by NMO-IgG has particular excitotoxic potential for neurons and oligodendrocytes. A focal increase of extracellular glutamate levels secondary to NMO-IgG – induced down-regulation of AQP4 may suffice to injure or kill oligodendrocytes that express calcium permeable glutamate receptors. Oligodendrocytes in the spinal cord and optic nerve, which are principal sites of demyelination in NMO, are particularly sensitive to changes in glutamate concentration.. Granulocytes attracted by complement, Null Killer cells and antibody dependent cellular cytotoxicity all adds to further tissue injury(115). It is plausible that upregulation of EAAT-2 or prevention of OAP formation could limit injury in NMO (34, 116).

Tissue injury in NMO IgG negative patients may be due to a yet unidentified antibody(117) or mediated by mechanisms other than autoantibodies e.g. cell mediated cytotoxicity(118). Similarities can be drawn to myasthenia gravis where a subset of Acetylcholine receptor antibody negative myasthenia was found to have another antibody- -MusK. Perhaps the same is possible for NMO. It could also be that the current techniques are unable to detect the low levels of antibody that may be pathogenic in uniquely vulnerable patients , explaining the higher morbidity in that group.

Depletion of AQP4 water channels in the plasma membrane would disrupt water homeostasis and promote edema. So far therapies targeting glutamate receptors have not been useful (in degenerative disorders) but it might be feasible to ameliorate tissue damage in both gray and white matter if therapeutic up regulation of EAAT2 can be achieved.

Another exciting prospect is the possibility of aquaporinopathies as a new disease category. There are a variety of aquaporins distributed widely in the body both within and out of the CNS. It is uncertain why disease manifestations of NMO are restricted only to the CNS.

Since its discovery in 2005, aquaporin- 4 antibodies have been demonstrated by several groups to have a high specificity and sensitivity for the diagnosis of NMO. Of the three methods used in the detection of the antibody, indirect immunofluroscence (NMO IgG), cell based assays and immuno-precipitation; the cell based assays have the highest sensitivity in (90%). This is closely followed by the immunofluroscence (86%) and immunoprecipitation(83%). Both cell based and immunoprecipitation assays had 100% specificity while indirect immunofluroscence have specificity of 91%(29). Wider availability of the tests will no doubt increase the amount of newly diagnosed cases. However who to test still remains a thorny issue. Ideally all patients with optic neuritis and transverse myelitis should be tested. In an increasingly cost constrained healthcare such broad guidelines may not be acceptable. It therefore seems reasonable that tests at the present time, be restricted to patients who have very severe optic neuritis, longitudinally extensive transverse myelitis, recurrent optic neuritis or myelitis. Another category of patients who might benefit from such tests are patients with atypical brain stem or hypothalamic changes. The need for testing in typical NMO is uncertain. Though a positive test would validate the diagnosis, a negative test does not invalidate it and treatment strategies will not be change.

It is uncertain if additional antibodies are present in currently sero-negative NMO patients. Newer techniques using samples from treatment naïve patients may reveal additional antibodies

Yet another important prospect is the utility of the antibody in monitoring the course of the disease. Preliminary results suggest that the AQP4 antibody levels rise before relapses and are reduced almost immediately with the use of intravenous steroids (66) Immunosuppressants particularly azathioprine seem to maintain the low levels in the few patients tested. Rituximab also drops the levels quickly but levels reappear within a few months. There seems to be no threshold value which will lead to a relapse. In fact in a few patients high levels of antibody do not seem to induce a relapse. This might mean that there might be other mechanisms that need to co-exist with high antibody levels to induce or trigger a relapse(66). These findings have important implications. If borne out by formal studies, one could envisage routine monitoring of NMO antibodies on a monthly basis looking for the reappearance following therapy and instituting pre-emptive therapy before relapses actually occur.

I have conducted 4 different studies looked at 3 aspects of NMO that were not well known before: epidemiology, long-term outcomes, and new treatments. Of the 128 patients 67 patients satisfied criteria for an optico spinal demyelinating syndrome. At a median follow up of 38 months 34 of these OSD patients satisfied current criteria for NMO. These combined with another 8 patients with NMO spectrum disorder formed the cohort of the prospective study of 42 patients, the largest prospective study to date.

81% of these patients were positive for the aquaporin-4 antibody. Treatments improved relapse rates, but did not improve disability. Ten (24%) patients died and all patients had some disability.

The current emphasis and interest in NMO treatment seems largely to be in preventing relapses which is a reasonable and laudable goal as relapses leave behind serious sequelae and the disability is acquired during attacks and not due to disease

progression as is typical of multiple sclerosis. However an equal emphasis has to be placed on improving the disability during an attack or terminating the attack. The present care of patients during a relapse need to be optimised. The rationale of using a short term intravenous course of steroids is derived from its use in multiple sclerosis where the disease is primarily demyelinating and recovery usually occurs irrespective of steroid treatment. However NMO relapses are serious and severe and are not just demyelination but involve tissue necrosis and loss. Therefore aggressive steroid therapy for at least five days with oral maintenance of prednisone is required in all cases in a relapse. Plasma exchange which is sparingly used has to be made widely available. The efficacy of plasma exchange in a variety of idiopathic inflammatory demyelinating disorders have been demonstrated by a controlled trial (39, 40). A subset of patients enrolled in this study with NMO had excellent outcomes. Much delay occurs from admission to being seen by a Neurologist and a decision for plasma exchange is taken, to the start of therapy. All patients diagnosed with NMO need to have a standardised treatment plan and algorithm that should automatically come into play when they are admitted.

Targeted blockade of interleukins, tumour necrosis factor - alpha and B cell activating factor (BAF) that mediate inflammation in the spinal cord might have potential future applications. Therapy to reduce glutamate mediated excitotoxicity can be combined with acute treatments with steroids and might limit the intensity of the inflammatory damage.

Preventative treatments for NMO unfortunately remain sparse. It remains conventional and makes economic sense that patients are initially tried on Azathioprine with or without steroids at an optimal dose. Thiopurine methyltransferase levels needs to be checked before initiation of Azathioprine as 10 % of patients do not metabolise the drug which cause serious liver toxicity. Both

rituximab and mycophenolate seems to be beneficial with quick suppression of CD20 positive B cells. However there is still a proportion of cases who remain refractory to these. Newer preventative therapies will hopefully emerge with time. No randomised trial has yet been conducted and though head to head controlled trials between, azathioprine, mycophenolate and rituximab are required to decide the first line agent. The rarity of the disease and the early disability make placebo controlled studies unethical. Till such time cost, availability, logistics, side effect profiles have to be considered in deciding the drug of first choice. Several of the drugs that are in use in rheumatological and other immunological disorders and MS could potentially be applied to NMO: these include tacrolimus, olmecruzimab and alemtuzumab.

Perhaps in the future the burden of disease will diminish be limited by the intensity of the first attack. Ideally all patients presenting with the index event of optic neuritis or myelitis with anti AQP4 antibodies would be instituted on effective immunosuppression. Serial antibody levels would help predict relapses which could be avoided by pre-emptive treatment. Therefore the only patients with serious disability due to NMO might be those that are left behind with serious sequelae after the very first event which we will be unable to predict. Large scale screening of the community for AQP4 antibodies is not a feasible option even in the future as the vast majority cases are sporadic and no genetic marker has yet been identified .

The prevalence of NMO, NMOSD and the combined group was estimated to be 4.37 and 3.49 and 7.86/million. The incidence was estimated to be 0.52, 0.7 and 1.22 /million/year respectively. These data suggest that there are at least 369 patients with NMO or NMOSD and 57 new patients/year in the UK. The various shortfalls of a hospital based study limit the epidemiological validity of the Merseyside data. A

population based study geographically defined area with adequate representation of all ethnic groups will be needed to truly answer the question if NMO is indeed less frequent in Caucasians.

Another outstanding clinical question is the existence of monophasic NMO. Long term follow up of such patients or a review of the published series of cases of monophasic NMO will help answer this. The differences between NMO antibody positive and negative groups, particularly the poorer outcomes in the latter, need to be validated in larger cohorts.

The exciting developments in NMO may have spin offs to multiple sclerosis whose pathogenesis which despite two centuries of research has remained still ambiguous and elusive. Several fundamental changes in scientific mindset need to occur if we are to make inroads into the understanding of multiple sclerosis. One of them is to delineate subpopulations of the illness. We should move away from the conventional view that multiple sclerosis is one disease –an all encompassing one - an explanation to all unexplained disease phenomena that have white matter lesions and an inflammatory CSF. Such an approach has long delayed the understanding of NMO and still continues to hinder varieties and subsets of opticospinal demyelination. Whether all OSD- U patients in my cohort will turn out into MS over time or remain a separate subgroup needs to be seen. The lumping of multiple sclerosis had its purpose at a time when therapies were ineffective or unavailable. In this new era of treatment of demyelinating disorders our goals should necessarily include clinical characterisation and immunogenetic classification of subtypes of demyelinating disease. Such an approach should bring to light several other lesser known or unknown demyelinating disorders which have been left in the shadows of an often irrevocable diagnosis of "a slightly atypical multiple sclerosis."

Chapter 8

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Chapter 9

Appendix

9.1 Kurtzke Expanded Disability Status Scale (EDSS)

❑0.0 - Normal neurological exam (all grade 0 in all Functional System (FS) scores*).

❑1.0 - No disability, minimal signs in one FS* (i.e., grade 1).

❑1.5 - No disability, minimal signs in more than one FS* (more than 1 FS grade 1).

❑2.0 - Minimal disability in one FS (one FS grade 2, others 0 or 1).

❑2.5 - Minimal disability in two FS (two FS grade 2, others 0 or 1).

❑3.0 - Moderate disability in one FS (one FS grade 3, others 0 or 1) or mild disability in three or
four FS (three or four FS grade 2, others 0 or 1) though fully ambulatory.

❑3.5 - Fully ambulatory but with moderate disability in one FS (one grade 3) and one or two FS
grade 2; or two FS grade 3 (others 0 or 1) or five grade 2 (others 0 or 1).

❑4.0 - Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite
relatively severe disability consisting of one FS grade 4 (others 0 or 1), or combination of
lesser grades exceeding limits of previous steps; able to walk without aid or rest some 500
meters.

❑4.5 - Fully ambulatory without aid, up and about much of the day, able to work a full day, may
otherwise have some limitation of full activity or require minimal assistance; characterized
by relatively severe disability usually consisting of one FS grade 4 (others or 1) or
combinations of lesser grades exceeding limits of previous steps; able to walk without aid
or rest some 300 meters.

❑ 5.0 - Ambulatory without aid or rest for about 200 meters; disability severe enough to impair
full daily activities (e.g., to work a full day without special provisions); (Usual FS equivalents are one grade 5 alone, others 0 or 1; or combinations of lesser grades usually
exceeding specifications for step 4.0).

❑ 5.5 - Ambulatory without aid for about 100 meters; disability severe enough to preclude full
daily activities; (Usual FS equivalents are one grade 5 alone, others 0 or 1; or combination
of lesser grades usually exceeding those for step 4.0).

❑ 6.0 - Intermittent or unilateral constant assistance (cane, crutch, brace) required to walk about
100 meters with or without resting; (Usual FS equivalents are combinations with more than
two FS grade 3+).

❑ 6.5 - Constant bilateral assistance (canes, crutches, braces) required to walk about 20 meters
without resting; (Usual FS equivalents are combinations with more than two FS grade 3+).

❑ 7.0 - Unable to walk beyond approximately 5 meters even with aid, essentially restricted to
wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair some 12 hours a day; (Usual FS equivalents are combinations with more than
one FS grade 4+; very rarely pyramidal grade 5 alone).

❑ 7.5 - Unable to take more than a few steps; restricted to wheelchair; may need aid in transfer;
wheels self but cannot carry on in standard wheelchair a full day; May require motorized wheelchair; (Usual FS equivalents are combinations with more than one FS grade 4+).

❑ 8.0 - Essentially restricted to bed or chair or perambulated in wheelchair, but may be out of

bed itself much of the day; retains many self-care functions; generally has effective use of
arms; (Usual FS equivalents are combinations, generally grade 4+ in several systems).

❑ 8.5 - Essentially restricted to bed much of day; has some effective use of arm(s); retains some
self-care functions; (Usual FS equivalents are combinations, generally 4+ in several systems).

❑ 9.0 - Helpless bed patient; can communicate and eat; (Usual FS equivalents are combinations, mostly grade 4+).

❑ 9.5 - Totally helpless bed patient; unable to communicate effectively or eat/swallow; (Usual FS
equivalents are combinations, almost all grade 4+).

❑10.0 - Death due to MS.

*Excludes cerebral function grade 1.

Note 1: EDSS steps 1.0 to 4.5 refer to patients who are fully ambulatory and the precise step
number is defined by the Functional System score(s). EDSS steps 5.0 to 9.5 are defined by
the impairment to ambulation and usual equivalents in Functional Systems scores are provided.

Note 2: EDSS should not change by 1.0 step unless there is a change in the same direction of at
least one step in at least one FS.

Sources: Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS).
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Publications arising from this work

REVIEW by Anu Jacob and Mike Boggild

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Neuromyelitis optica

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Neuromyelitis optica also known as Devic's disease is an uncommon, immune mediated demyelinating condition of the central nervous system affecting predominantly the spinal cord and optic nerves. Since 1894 when Eugene Devic summarised 17 known cases of optic neuritis and myelitis the relation between neuromyelitis optica and multiple sclerosis (MS) has been controversial. The overlapping clinical features and the propensity for patients with neuromyelitis optica to express a range of auto-antibodies can result in misdiagnosis, of both MS and other autoimmune disorders. However, clinical, radiological, and immunopathological studies suggest neuromyelitis optica is distinct from MS. The recent identification of an apparent disease specific antibody—termed NMO-IgG (against the aquaporin-4 water channel) implicates humoral immunity.[2, 3] This further differentiates the disorder from MS and suggests that treatment to prevent relapses should be aimed primarily at humoral B cell mediated immunity if a pathogenic role for NMO-IgG is confirmed.

EPIDEMIOLOGY

Neuromyelitis optica is an uncommon disorder in Western populations; based on observed cases among a population of 3 million over 10 years in North West England we estimated a minimum incidence of 0.4/million/year and a prevalence of 4/million, representing only one in 200 patients with demyelinating disease in this population.[4] This contrasts with a much higher incidence in populations of Asian,

Afro-Caribbean, and South American descent implying underlying genetic mechanisms in the expression of demyelinating disease. In all populations there is a strong female predominance, of >3:1 compared with males.[4,5] The mean age of onset is around 40, although cases have been reported in childhood.

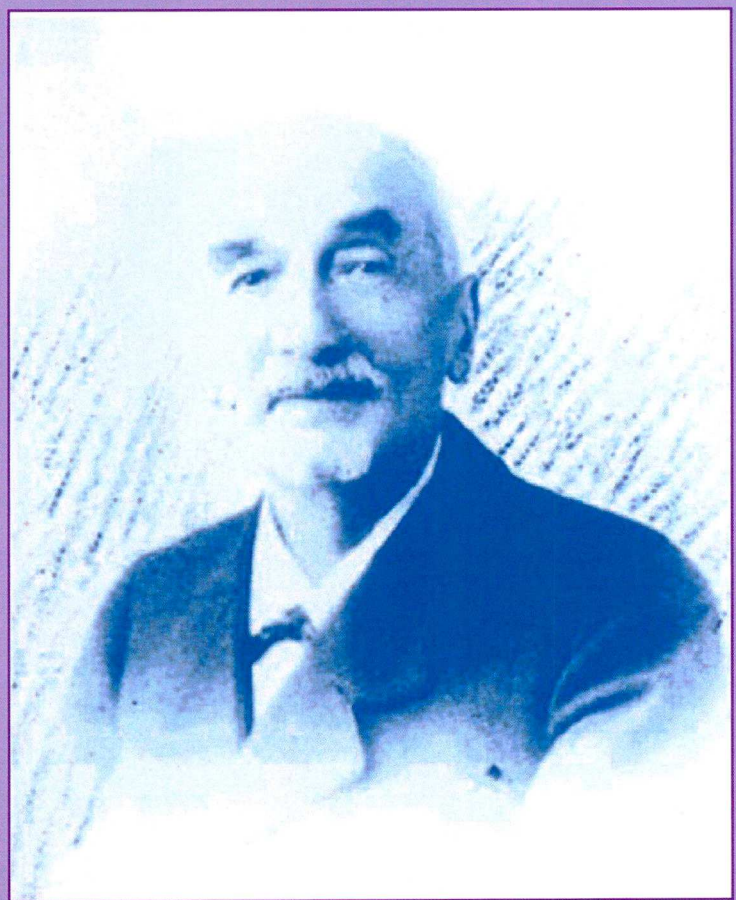
CLINICAL FEATURES

The cardinal clinical features of the disorder are transverse myelitis, which is often longitudinally extensive, and optic neuritis. These two index events can occur simultaneously, in rapid succession, or they can be separated by many years. The optic neuritis can be unilateral or bilateral. Some patients have repeated episodes of optic neuritis before myelitis occurs and vice versa (the nomenclature of the disease at this stage is relapsing myelitis or relapsing optic neuritis). Most of those affected (>80%) go on to have repeated relapses (relapsing NMO) though a minority may have only the index events (monophasic disease). Relapses are generally more disabling than those in patients with typical MS. Whereas in MS disability develops largely in the progressive phase of the disease, in neuromyelitis optica disability is acquired as a consequence of relapses; progressive disability without relapses is rare in our experience.

In white populations most patients presenting with optic neuritis and myelitis are likely to have MS rather than neuromyelitis optica. Features which may help distinguish the disorder from MS clinically are the more severe myelitis, optic neuritis with poor recovery, and no involvement of other parts of the neuraxis. However the disease spectrum may be wider than currently accepted (see discussion below).

A variety of diagnostic criteria for the disorder have been formulated and are summarised elsewhere.[6] None is perfect and it is likely that they will be revised in the light of emerging clinical and laboratory data. In general we would consider the diagnosis in the presence of:

Clinical, radiological, and immunopathological studies suggest neuromyelitis optica is distinct from MS



Eugène Devic (1858–1930). Image courtesy of Professor Christian C , Hôpital Neurologique Pierre Wertheimer, Lyon, France.

Eugène Devic was born in 1850 in La Cavalerie, a small village in Aveyron, in southern France. He trained at the medical college of Lyon and later worked on a variety of subjects, and was especially interested in typhoid fever and cardiovascular diseases. In the field of neurology, he wrote about infantile chorea, "polyneuritic psychosis", mental disorders in typhoid fever, cerebral glioma, corpus callosum tumours, meningeal angiosarcoma, and post-hemiplegic contracture. In December 1892 he saw a 45 year old French woman for intractable headache and depression with "general weakness" at the Hôtel-Dieu Hospital of Lyon. On 27 January urinary retention appeared, followed by complete paraplegia and bilateral blindness. She died from bedsores on 4 March 1893. The case and pathological examination, which confirmed lesions in the spinal cord and optic nerves, was presented as a clinicopathological study at the First Congress of Internal Medicine in Lyon in 1894. Here Devic mentioned 16 other similar cases reported in Europe and the USA. These 17 cases were studied in detail in the doctoral thesis of Fernand Gault –"*De la neuromyélite optique aiguë*"– in the same year. Neuromyelitis optica was called "Devic's disease" after Acchiote proposed this eponym in 1907. In his paper Devic named the disorder "neuro-myélite optique" or "neuroptico-myélite". The two cardinal questions he raised more than a century ago "Why such a peculiar localisation?" and "What is the intimate nature of the process?" still remain largely unanswered.[1]

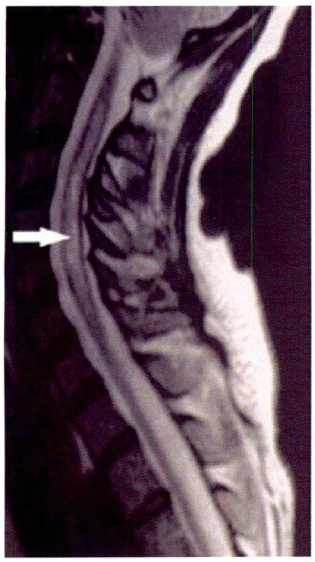


Figure 1
Sagittal T2 MRI appearances of longitudinally extensive cervical myelitis (arrow), usually centrally located within the cord.

- longitudinally extensive myelitis (usually more than three vertebral segments)
- optic neuritis
- normal brain MRI, or if abnormal, atypical for MS—see below.

The prognosis also differs from MS. Early reports suggested a five year survival of 68%, death often resulting from severe spinal cord disease and respiratory compromise.[5] More recent series suggest a better outcome, possibly reflecting better case ascertainment or treatment. However there is no doubt that disability is acquired earlier in neuromyelitis optica than MS; this and a mean relapse rate of around two per year make early diagnosis and therapy imperative.

RADIOLOGY

The most characteristic radiological feature is a longitudinally extensive cord lesion, extending often over three or more spinal segments and expanding the cord (fig 1). This is usually hypointense on T1 and hyperintense on T2 MRI. Lesions are centrally situated within the cord and patchy contrast enhancement is often seen. Occasionally lesions can be identified in the optic nerves. Though classically NMO has been defined by lack of brain lesions or symptoms, it has increasingly been noted that up 60% of patients with otherwise typical relapsing NMO (many with positive NMO-IgG) can have lesions on brain MRI. These range from extension of high cervical cord lesions into the brain stem, diencephalic, brainstem or cerebral lesions "atypical" for MS and in minority MS-like lesions. However all these patients have long cord lesions which seems to be a specific feature, distinguishing these cases from MS.[9]

The most characteristic radiological feature is a longitudinally extensive cord lesion, extending often over three or more spinal segments and expanding the cord

LABORATORY INVESTIGATIONS

Cerebrospinal fluid acutely may reveal a prominent pleocytosis of either lymphocytes or neutrophils and raised protein. In contrast to MS, there are usually no oligoclonal bands (in over 80%). Lennon and co-workers at the Mayo clinic recently reported the discovery of NMO-IgG, which may be the first "disease specific" antibody in CNS demyelinating disease.[3] The antibody, identified initially from Western blots in patients screened for possible paraneoplastic antibodies, is reported to have a sensitivity of 73% and a specificity 91% for neuromyelitis optica and was also positive in a significant proportion of patients deemed to be at high risk of neuromyelitis optica (that is, patients with recurrent optic neuritis or myelitis). Despite the apparent association of NMO-IgG with neuromyelitis optica, independent confirmation of this finding and indeed evidence of pathogenesis is still awaited. The Mayo group has also recently reported that the target antigen for NMO-IgG appears to be the aquaporin-4 water channel, located in astrocytic foot processes at the blood-brain barrier.[2] To date, testing for NMO-IgG is only available through the Mayo clinic (Rochester, USA; at a cost of $500/sample). If the role of the antibody is confirmed and the assay becomes readily available, the hope is clearly that the relation between neuromyelitis optica and "neuromyelitis optica spectrum" disorders (see below) will be clarified, and predictive testing for neuromyelitis optica in patients with isolated myelitis or severe optic neuritis may be possible.

A range of positive auto-antibodies (including ds-DNA) have been reported in up to 40% of patients.[4] This can give rise to diagnostic difficulties. We would consider these to be epiphenomena occurring in the context of disordered humoral immunity. However there are reports of patients with unambiguous systemic lupus erythematosus, Sjögren's syndrome, and mixed connective tissue disease who have developed neuromyelitis optica. Whether they have two separate autoimmune diseases, or neuromyelitis optica is a consequence of the primary disorder, is impossible to determine clinically. Testing for NMO-IgG and pathological examination in such cases may be able to clarify this.

PATHOLOGY

Extensive necrosis, demyelination, and often cavitation across multiple spinal cord segments, involving grey and white matter with perivascular infiltrates, prominent macrophages, eosinophils, and vascular hyalinisation is typical. Deposition of complement in a ring

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pattern on the outer surface of blood vessels and in a rosette perivascular pattern has been elegantly demonstrated. Prominent perivascular IgG reactivity and IgM deposition in a rosette pattern implicate these as sites of immune mediated damage.[8]

TREATMENT

The rarity of the condition inevitably limits the evidence for therapeutic interventions. As in most immune mediated disorders management consists of treatment of relapses, therapy for the underlying disease, symptom control, and rehabilitation. For the general neurologist managing a patient with neuromyelitis optica the approach to relapses and indeed underlying disease therapy is perhaps most comparable to that of the more common antibody mediated disorder myasthenia gravis.

MANAGEMENT OF RELAPSES

High dose corticosteroids and supportive care remain the mainstays of management of relapse. In view of the severity of relapses and likely need for maintenance treatment our policy is to follow a course of intravenous methylprednisolone (1 gram daily for 3–5 days) with a gradual taper of oral prednisolone over several months, from an initial dose of 1 mg/kg/day. An alternate day maintenance dose of the order of 10–20 mg prednisolone is generally our target in patients with relapsing disease.

A minority of patients fail to respond to adequate steroid therapy or relapse rapidly and in such cases there is a role for therapeutic plasma exchange. We consider it early—within weeks of symptom onset. In the North American randomised trial of plasma exchange in severe demyelinating events, patients with neuromyelitis optica were overrepresented among the responders, with a 60% response rate (versus 6% overall for sham exchange). In this study plasma exchange was undertaken within three months of onset of relapse.

PREVENTION OF RELAPSES

Most patients follow a relapsing course, often acquiring substantial disability within two or three relapses. Immunosuppression appears to reduce the relapse rate. The first report of successful treatment was a series of seven patients treated with prednisolone (tailing dose as above) and azathioprine (at 2.5–3 mg/kg). In our initial case series of 42 patients, relapse rates were reduced by over 80% in patients established on immunosuppressive therapy (most frequently azathioprine). This has therefore remained our initial therapy option in patients with relapsing, but reasonably stable, disease. For patients intolerant of azathioprine, mycophenylate mofetil is a reasonable alternative (but without any evidence base), with the possible advantage of more rapid onset of action.

In patients who have "breakthrough" disease on azathioprine, or who present with frequent severe relapses, more aggressive immunosuppression may be necessary. Recent small case series have reported on the successful use of rituximab (a B cell depleting monoclonal antibody) and mitoxantrone. We have used both of these agents in small numbers of patients without complications. Interferon beta, the mainstay of treatment in relapsing MS, does not appear to be effective.

PRACTICE POINTS

- Although neuromyelitis optica is uncommon it is a rapidly disabling yet treatable disorder.
- Early recognition and diagnosis followed by prompt, carefully supervised immunosuppressive treatment in relapsing patients is paramount. A blind, quadriparetic, ventilator dependent person, from a treatable disorder, is a tragedy that one should strive to avoid at all costs.
- Management appears distinct from that of MS and should probably be in the hands of clinicians with an interest in demyelinating disease.

SYMPTOM CONTROL AND REHABILIATION

Pain, stiffness, bladder, and bowel symptoms need to be tackled. Tonic spasms seem to be much commoner than in MS and in our experience usually respond to carbamazepine. Rehabilitation, physiotherapy, mobility, and visual aids are often needed. Some patients with high cervical cord lesions will need long term home ventilatory support. There is a UK based self-help group (telephone +44 (0)151 529 6100) and a patient friendly website (http://www.thewaltoncentre.co.uk/patients/Neuromyelitis_Optica.html)

THE WIDENING SPECTRUM OF NEUROMYELITIS OPTICA

There may be a number of related disorders, a full discussion of which is beyond the scope of this review. Patients with idiopathic relapsing myelitis, Asian "optico-spinal" MS, and chronic relapsing

inflammatory optic neuropathy may form part of the "neuromyelitis optica spectrum". We have seen several patients presenting with severe myelitis without visual symptoms but delayed visual evoked responses, some of whom have subsequently developed optic neuritis. It seems likely that such patients have neuromyelitis optica although they fall outside current criteria for the disorder. Traditionally patients with clinical or radiological findings outside the optic nerves and spinal cord have also been excluded from the diagnosis of neuromyelitis optica. There are however recent reports of patients with clinically typical neuromyelitis optica who have developed brain lesions on MRI. Interestingly these patients have been shown to have positive NMO-IgG, and histopathology (of the brain lesions) similar to classical neuromyelitis optica, widening the spectrum still further. More studies with a validated disease marker in the near future should clarify these relationships. Genetic links between neuromyelitis optica and MS have been hypothesised and will perhaps open a window to the better understanding of both conditions.[9]

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We thank Ms Karen Reeves at the ABN and Neurologists around the UK who have referred patients to the UK NMO study. The UK NMO study is an ongoing registry of NMO and related diseases, recruited by the British Neurological Surveillance Unit (BNSU), through which to date over 70 cases have been identified and are being followed.

This article was reviewed by Professor Reinhard Hohlfeld, Munich, Germany.

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Review article

Neuromyelitis optica: Changing concepts

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Abstract

Neuromyelitis optica (NMO; Devic's disease) and the NMO spectrum disorders are idiopathic inflammatory demyelinating disorders that affect the central nervous system and have a predilection for optic nerves and spinal cord. The identification of NMO-IgG as a disease-specific marker and aquaporin 4 as the target antigen has renewed interest in NMO. Based on current data, we suspect that autoantibodies arising from peripheral B cells bind to aquaporin 4 expressed on astrocyte foot processes on the abluminal surface of microvessels, activate complement and initiate inflammatory demyelination and necrosis. The development of animal models and further analysis of the association of NMO-IgG with disease severity and treatment response will elucidate the pathobiology of NMO.

Keywords: Neuromyelitis optica; Devic's; Aquaporin; Multiple sclerosis

Contents

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1. Introduction

Neuromyelitis optica (NMO) is an inflammatory demyelinating disease of the central nervous system (CNS) that most commonly targets the optic nerves and spinal cord selectively. Its historical roots begin with Allbutt who in 1870 reported a patient with a "sympathetic disorder of the eye" after an acute myelitis (Allbutt, 1870). Twenty four years later, Devic and his student Gault summarized 16 cases from the literature in addition to one of their own and the syndrome came to be eponymously called Devic's disease (Devic, 1894). For much of the 20th century, NMO was considered to be a severe monophasic syndrome characterized by bilateral optic neuritis (ON) and myelitis occurring in rapid succession. Subsequent studies included patients with less severe clinical attacks, unilateral ON and symptoms separated by months or years. It became a matter of debate whether NMO was a distinct disease or a peculiar variant of multiple sclerosis (MS) and whether it included patients with recurring disease. Based on emerging conventions of MS as being a disease "disseminated in time and space" NMO too was soon entrenched as a form of MS.

In recent years, medical opinion has shifted because of a number of developments. Firstly, unlike MS, NMO is not associated with brain lesions at disease onset in most patients; nonetheless, brain lesions do occur over time in the majority of patients, and their recent characterization has proven informative as to the pathogenesis of the disease. Secondly, large clinical series published over the past decade have revealed that most patients with NMO have longitudinally extensive transverse myelitis (LETM) defined by an MRI lesion extending contiguously over three or more vertebral segments, which is hardly ever occurs in MS (Cabre et al., 2001; de Seze et al., 2003; Ghezzi et al., 2004; Nakashima et al., 2006; Papais-Alvarenga et al., 2002; Wingerchuk et al., 1999, 2006). Thirdly, neuropathologic studies demonstrate that although demyelination is present, NMO is characterized by distinctive "vasculocentric" pathology with prominent perivascular immunoglobulin deposition and evidence of activation of complement lytic pathway, invoking B cell participation in the disease process (Lucchinetti et al., 2002; Wingerchuk, 2006). Lastly, a highly specific serum antibody (NMO-IgG) (Lennon et al., 2004) has been found in patients with NMO but not in patients with "prototypic" MS or in other conditions characterized by optic neuropathy and myelopathy. These clinical, radiological, pathological and immunological data provide convincing evidence that NMO spectrum disorders are distinct from MS. Nonetheless, while apparently distinct, the boundaries that delimit NMO from MS are not yet well defined. Whether all relapsing "optic-spinal" forms of MS, as have been commonly recognized in Asia, are the same entity as NMO described in Western countries is a continuing source of debate.

The recent discovery that NMO-IgG reacts specifically with aquaporin 4 (AQP4) (Lennon et al., 2005) has opened new avenues for the understanding of the pathogenesis of idiopathic inflammatory demyelinating disease; it is the first instance in which a specific target for an immune reaction resulting in an inflammatory demyelinating disease in humans has been identified.

We review the evolving epidemiological, clinical, imaging and immunological research that suggests that the clinical spectrum of the disease is broader than previously recognized, emphasizing the NMO-IgG biomarker. NMO-IgG is now utilized as a clinical test for this disease and promises to provide substantial insight into the pathogenesis of NMO. Finally, we discuss the preferred therapeutic options for this condition, which differ substantially from those for MS.

2. Epidemiology

Relapsing NMO has a female to male ratio of 5:1. Monophasic NMO, by contrast, affects both sexes equally. The median age of onset in Caucasians is late in the fourth decade(Wingerchuk et al., 1999), which is considerably older than that of MS. Pediatric cases have been reported and may be either monophasic or relapsing (Arabshahi et al., 2006; Domingues et al., 2004; Jeffery and Buncic, 1996; Jouhadi et al., 2004; Milani et al., 2004). Non-Caucasians (African, Hispanic and Asian) are over-represented among NMO patients when compared to MS patients; however, Caucasians comprise the majority in series from Western countries. In Japan, 15–40% of cases of demyelinating disease are "opticospinal" (Kira, 2003). Nevertheless the terms 'optico spinal' MS (OSMS) and NMO, may define overlapping, but not identical groups of patients. Many Asian investigators apply the term OSMS to patients with ON and myelitis who do not have long spinal cord lesions whereas we would classify such patients as having prototypic MS; our current view is that NMO is a subset of optico-spinal MS in Asia. This is a common source of confusion in comparing data from Western and Asian series.

The incidence and prevalence of NMO has been difficult to estimate because it is still an under-recognized illness and diagnostic techniques such as spinal MRI and availability of NMO-IgG testing are not readily available in all geographic regions.

3. Genetics

It is uncertain whether genomic variation accounts for differences in susceptibility to NMO. Instances of familial NMO have been reported: identical twin sisters, one who developed the illness at age 24 and the other at age 26

(McAlpine, 1938); two sisters with bilateral ON followed by myelitis at 2 and 3 years (Ch'ien et al., 1982); two Japanese sisters aged 62 and 67 (Yamakawa et al., 2000); and two sisters of Spanish–American ancestry, who developed NMO at ages 26 and 28 (Keegan and Weinshenker, 2000) are among these cases.

HLA association studies in NMO are few and have primarily been conducted in Japan. Among Japanese patients, HLA *DRB1*1501*, the allele that is most strongly associated with MS in western countries, is not associated with OSMS, although it is associated with Japanese "classical" MS (Kira, 2003). HLA *DP*0501* has been reported to be over-represented in Japanese patients with OSMS (Yamasaki et al., 1999); however, the high frequency of this allele in the general Japanese population complicates the analysis of the putative association in this population. Recently, over-representation of the *DPB1*0301* allele among non-OSMS population has been reported as a confounding factor in the interpretation of the *DP*0501* reported primary association (Fukazawa et al., 2006).

4. Clinical features

The *sine qua non* of NMO is the simultaneous or consecutive occurrence of ON (unilateral or bilateral) and acute LETM. ON in NMO tends to be more severe and leaves a greater impairment compared to attacks of ON in the context of MS. Clinical features such as ocular pain, visual field deficits and positive phenomena do not differ substantially (Wingerchuk et al., 2006).

Spinal cord relapses, unlike those of MS, typically present as a complete transverse myelitis with bilateral motor weakness, a sensory level and sphincter dysfunction; prominent dysesthetic and even radicular pain are common. Brain stem involvement can occur, usually as an extension of a severe cervical myelitis, and may cause hiccoughs, intractable nausea, or respiratory failure (Misu et al., 2005). Paroxysmal tonic spasms are more common in NMO compared with prototypic MS. This pathognomonic symptom of demyelination, believed to represent ephaptic transmission across demyelinated axons, clearly place NMO in the category of a demyelinating disease (Wingerchuk et al., 1999).

After the initial index events of ON and myelitis that define NMO, either no further events take place (monophasic course) or, as occurs in greater than 80% of the patients, relapses of ON and myelitis occur, interspersed by intervals of months or years. Among patients with NMO, a relapsing course is associated with female sex, older age at onset, longer time interval between index events, and the presence of systemic autoimmunity. (Wingerchuk et al., 1999; Wingerchuk and Weinshenker, 2003)

Many NMO patients have other auto-immune diseases, the most frequent of which are thyroid disease, systemic lupus erythematosus (SLE) and Sjögren's syndrome (SS). Even more frequently, non-organ specific antibodies, such as antinuclear antibodies or SSA antibodies, are detected in the absence of clinical symptoms and signs of their associated systemic illnesses. Patients with SLE or SS who have never experienced ON or myelitis are uniformly NMO-IgG seronegative, whereas those with ON or myelitis are usually seropositive. This has led us to conclude that NMO-IgG is a specific marker for the ON and myelitis (NMO spectrum disorders) occurring in this conditions, rather than a nonspecific coexisting serological finding associated with SS or SLE. (Pittock et al., 2006b)

The prognosis is often poor for patients with relapsing disease. Unlike MS, most attacks are moderate or severe; remissions are often incomplete and neurologic disability accumulates in a step-wise fashion. More than half of patients will develop severe visual loss in at least one eye and or inability to ambulate without assistance within 5 years of disease onset. In the original Mayo Clinic cohort, the 5 year-mortality rate in relapsing patients was 32%. All patients died because of respiratory failure associated with attacks of myelitis. (Wingerchuk et al., 1999). Patients seen at the Mayo Clinic may have a more severe course than average, and ascertainment bias may have influenced this conclusion, although

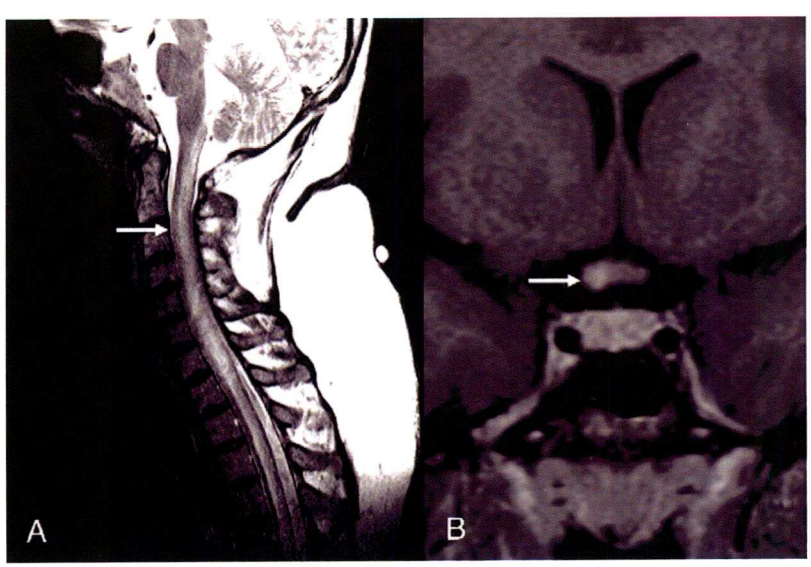

Fig. 1A T2 weighted cervical spinal cord MRI in a patient with NMO showing a longitudinally extensive (>3 vertebral segments) lesion (arrow). 1B: Coronal T1-Weighted brain MRI of NMO patient showing enlargement and gadolinium enhancement of the right side of the optic chiasm (arrow).

most series are consistent that attacks of NMO are generally more severe than of MS.

5. Neuroimaging

Almost invariably, if a spinal cord MRI scan is performed at an appropriate interval after an acute attack (within days to weeks), it reveals a central cord lesion extending over three or more vertebral segments (Fig. 1A). Spinal cord MRI is the most specific diagnostic test for NMO aside from NMO-IgG serological testing. Acute imaging commonly reveals cord edema and gadolinium enhancement, the latter of which may persist for several months. On follow-up MRI studies, cord atrophy and a cavity resembling a syrinx may be present; lesions may resolve entirely, or may leave only atrophy in their wake.

Brain MRI often reveals gadolinium enhancement of the optic nerve during an acute ON episode, of variable extent and occasionally extending into the chiasm from the globe. (Fig. 1B) At disease onset, the brain parenchyma is usually normal or may demonstrate few nonspecific subcortical white matter changes that usually do not fulfill Barkhof radiological criteria for MS. Pittock et al. reviewed 60 NMO patients and found brain MRI lesions in 36 patients (60%). Most were nonspecific, but 6 patients (10%) had MS-like lesions, usually asymptomatic. Another 5 patients (8%), mostly children, had diencephalic, brainstem or cerebral lesions, atypical for MS. In a subsequent study of 120 patients, 8 patients were identified who had distinctive magnetic resonance imaging abnormalities in the hypothalamic and periventricular areas that corresponded to brain regions of high AQP4 expression, the target antigen for NMO-IgG (Pittock et al., 2006a,c). In some cases, brain abnormalities were associated with transient encephalopathy or with endocrinopathies when the hypothalamic–pituitary axis was involved. (Poppe et al., 2005; Vernant et al., 1997). Symptomatic brain lesions, originally believed to exclude the diagnosis, are no longer an exclusionary criterion in the most recently proposed diagnostic criteria for NMO (Table 1) (Wingerchuk et al., 2006).

Analysis of normal-appearing brain tissue (NABT) using diffusion tensor imaging has shown abnormal diffusion in patients with NMO. It is postulated that this could be secondary degeneration caused by lesions in the spinal cord and optic nerve (Yu et al., 2006).

6. Cerebrospinal fluid

CSF examination obtained during a relapse often reveals elevated total protein and on some occasions (perhaps 10% of attacks) reveals a prominent pleocytosis up to $50–1000 \times 10^6$ WBC/L, which may occasionally include or be dominated by neutrophils. When present, this is a useful distinguishing feature from MS (Wingerchuk et al., 1999). CSF pleocytosis in relapses of MS rarely exceeds 50×10^6 WBC/L (Zaffaroni, 2004; Wingerchuk et al., 1999). Oligoclonal bands which are present in approximately 90% of patients with an established diagnosis of MS are present in fewer than 20% of patients with NMO (Wingerchuk et al., 1999). Eosinophils may also be found in the CSF in NMO (Correale and Fiol, 2004).

Other differences have been noted between MS and NMO. Matrix metalloproteinase-9 in CSF is higher in MS compared to NMO (Mandler et al., 2001). Although the total IgG concentrations were elevated in the CSF of patients with NMO and MS, IgG1 levels and index were elevated only in patients with MS and not in patients with NMO. The lower CSF IgG1 level in NMO was interpreted to indicate a lesser Th1 autoimmune response than in MS (Nakashima et al., 2004).

Ishizu et al. evaluated sixteen cytokines/chemokines simultaneously in CSF supernatants from 20 OSMS and 20 typical MS (at relapse) patients and compared the findings with those from 19 controls with spinocerebellar degeneration. The OSMS MS patients had elevated levels of interleukin (IL)-17 and IL-8, which might explain the increased neutrophil presence in the central nervous system in NMO. Moreover, both the length of the spinal cord lesions on MRI and the CSF/serum albumin ratio correlated with the cytokine levels (Ishizu et al., 2005). Correale et al. have reported increased numbers of IL-5, IL-6, IgG, and IgM secreting cells in the CSF that are MOG-specific in patients with NMO compared to patients with RRMS, SPMS and healthy subjects (Correale and Fiol, 2004).

Chemokine levels (CXCL10/IP-10, CCL17/TARC, CCL2/MCP-1, and CCL11/Eotaxin) in the cerebrospinal fluid did not differ between NMO and MS. Similarly there was no difference in cerebrospinal fluid levels of CD26 (a dipeptidyl peptidase-IV highly expressed on Th1 cells), and CD30 (a member of the tumor necrosis factor/nerve growth factor receptor superfamily preferentially expressed on Th2 cells) between NMO and MS (Narikawa et al., 2005). However in another study CSF Eotaxins (selective eosinophil chemoattractants and activators) Eo-2, Eo-3 and ECP (eosinophil cationic protein) levels were significantly higher in NMO patients compared to RRMS, SPMS and healthy controls (Correale and Fiol, 2004).

Table 1

Proposed diagnostic criteria for neuromyelitis optica (Wingerchuk et al., 2006)

Optic neuritis
Acute myelitis
And at least two of three supportive criteria
1. Contiguous spinal cord MRI lesion extending over 3 vertebral segments
2. Brain MRI not meeting diagnostic criteria for multiple sclerosis
3. NMO-IgG seropositive status

7. Pathology

The hallmark of NMO pathology is the presence of necrotic spinal cord lesions involving both gray and white matter, often resulting in cavitation, as well as the presence of vascular hyalinization (Cloys and Netsky, 1970; Mandler et al., 1993; Prineas and McDonald, 1997). Lucchinetti et al. examined the spinal cord of nine autopsied cases of NMO and found a prominent eosinophil infiltration in active NMO lesions in addition to demyelination and necrosis with cavitation. A single autopsied case from a cohort of Canadian aboriginals, 5 of 7 of whom shared a NMO phenotype, also had extensive infiltration of eosinophils in the spinal cord lesions (Mirsattari et al., 2001). Lucchinetti et al. also described perivascular immune complex

deposition in a characteristic "rim" and "rosette" pattern (Lucchinetti et al., 2002) (Fig. 2). Based on these findings, the investigators proposed that NMO was a humoral disorder targeting the perivascular region. A similar pattern of immunoglobulin deposition and complement activation was recently described in patients with Japanese OSMS (Misu et al., 2005). Furthermore, the pathology of cavitary cerebral lesions from two NMO patients was similar to that observed in optic nerve and spinal cord NMO lesions, strongly suggesting a common pathogenesis (Jacobs et al., 2006; Nakamura et al., 2005).

8. Immunology

8.1. Discovery of NMO-IgG

In 1998, the observation that patients with NMO frequently had multiple autoimmune disorders and a variety of non-organ-specific autoantibodies prompted a search for a specific autoantibody marker of NMO. Sera of established NMO patients or those who were at a high risk of developing it (e.g. recurrent LETM or recurrent ON) were screened for IgG that binds selectively to CNS tissues using an indirect immunofluorescence assay optimized in Mayo Clinic's Neuroimmunology Laboratory in 1994 (Lennon, 1994; Lennon et al., 2004).

After testing the first few NMO patients' sera, a recurring pattern of immunostaining of mouse cerebellum and midbrain was detected that was named "NMO-IgG". This pattern was identical to that of an unclassified IgG of unknown clinical significance that the Laboratory had documented photographically in the preceding 2 years. Review of the clinical information for seropositive patients, whose undiagnosed neurological disorder had prompted submission of their serum for paraneoplastic autoantibody evaluation from across the USA, surprisingly revealed that 12 of 14 patients had a clinical presentation consistent with NMO or a limited version thereof (recurrent myelitis or recurrent ON).

An independent pathologic study from the Mayo Clinic had meanwhile recognized immunohistochemical pattern of immunoglobulin and complement deposition detected around small vessels of autopsied spinal cord tissues of patients with NMO-IgG (Lucchinetti et al., 2002). This pattern was reminiscent of the pattern of immunostaining of serum from NMO patients to the abluminal surface of penetrating microvessels in the mouse brain substrate.

A larger prospective survey of sera from patients with clinically definite NMO or a syndrome deemed to be at high risk for progression to NMO was undertaken (Lennon et al., 2004). Patients with classical MS that initially involved spinal cord and optic nerves, and patients with paraneoplastic autoimmune

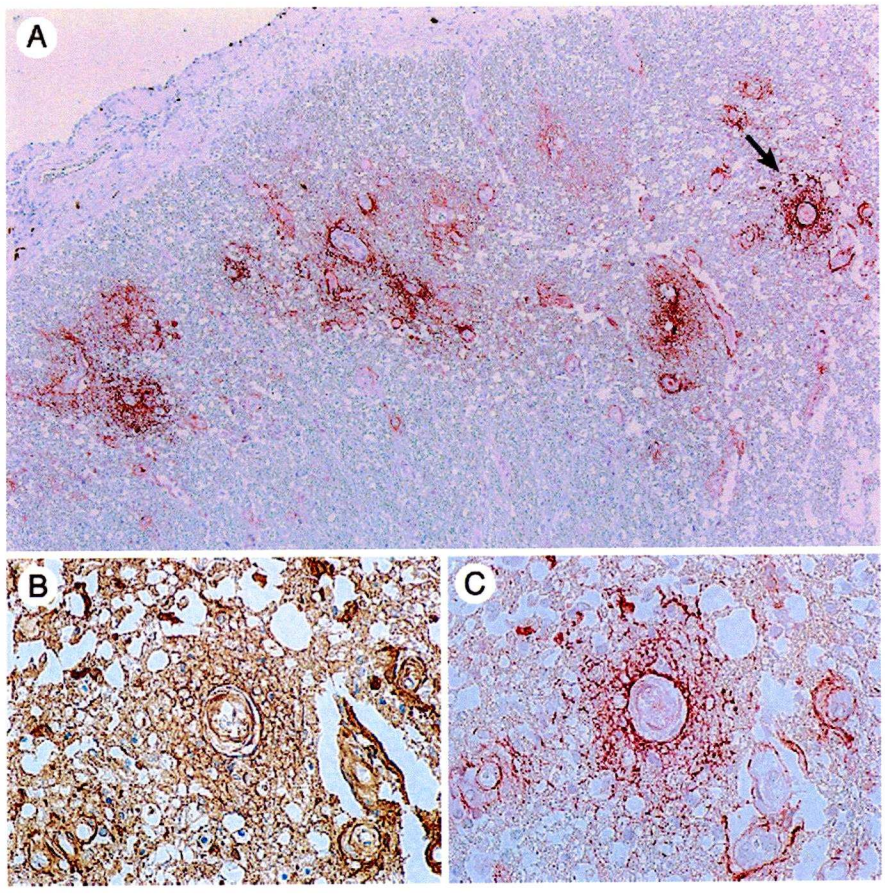

Fig. 2. Immunopathology of NMO. A. Complement activation products are deposited in a vasculocentric rim and rosette pattern (Immunocytochemistry for C9neo antigen (red). B/C. Higher magnification demonstrates colocalization of immunoglobulin (B, Immunocytochemistry for IgG) and complement (C, immunocytochemistry for C9neo antigen) on sequential sections.

disorders, myelopathies and miscellaneous disorders were evaluated as controls. Two independent readers blinded to diagnoses were 100% concordant in their interpretation. In the cerebellum and midbrain, NMO-IgG bound in a linear pattern along pial membranes, extending into the Virchow–Robin spaces, the abluminal surface of cerebral microvessels, and the subpial region with a mesh pattern (Fig. 3). Thirty three (73%) of 45 patients with clinically defined NMO were seropositive. Only 2 of 19 patients with classical MS and none of 56 individuals with other neurological or systemic autoimmune diseases were positive. Thus, NMO-IgG was 73% sensitive and 91% specific in distinguishing NMO from MS. Patients with "typical" Asian OSMS, Japanese classical MS and control patients with cerebral infarction, independently diagnosed by investigators at Tohoku University Medical Center in Sendai, Japan were tested at Mayo Clinic blinded to the diagnoses. Seven of 12 patients with OSMS were seropositive. None of the five patients with classical "Western" MS and none of the five control individuals with cerebral infarcts were seropositive. The sensitivity (58%) and specificity (100%) of NMO-IgG were comparable to the results in North American patients with NMO. This study suggested, as previously suspected on clinical grounds, that typical Asian optic-spinal patients had the same disease as NMO in western countries (Lennon et al., 2004).

The specificity of NMO-IgG has been validated at several international centers. Various studies presented at the 2006 European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) address the sensitivity and specificity of autoantibodies to AQP4 that were tested with a variety of different assays (Table 2).

Whether NMO-IgG titer correlates with disease severity, attack severity or favorable response to therapy is unknown. Typically, NMO-IgG is detected at the first attack of myelitis or ON, suggesting that the antibody is more likely an integral part of the pathogenesis of the disease rather than an epiphenomenon of the tissue injury, but longitudinal data are limited and preliminary.

8.2. Spectrum of neurological disorders in which NMO-IgG has been identified

NMO-IgG is not restricted to typical NMO. It has been identified in "NMO-related diseases" which at present consist of four groups:

8.2.1. Limited forms of the disease

These include recurrent myelitis without evidence of ON and recurrent ON without evidence of myelitis.

The NMO-IgG seropositivity rate in recurrent LETM approaches that of definite NMO. In a prospective study of 29 consecutive patients evaluated at Mayo Clinic with a single event of longitudinally extensive "idiopathic" transverse myelitis, 40% were seropositive (Weinshenker et al., 2006a). Of 9 seropositive cases followed for 1 year or longer, 55% (5 patients) had a relapse of myelitis (4 patients) or developed ON (1 patient) within 1 year of follow-up; an additional seropositive patient developed ON in the second year of follow-up. In contrast, no seronegative patient had a subsequent neurological event. Scott et al. have studied the incidence of NMO-IgG in acute partial transverse myelitis with lesions less than 3 segments. They

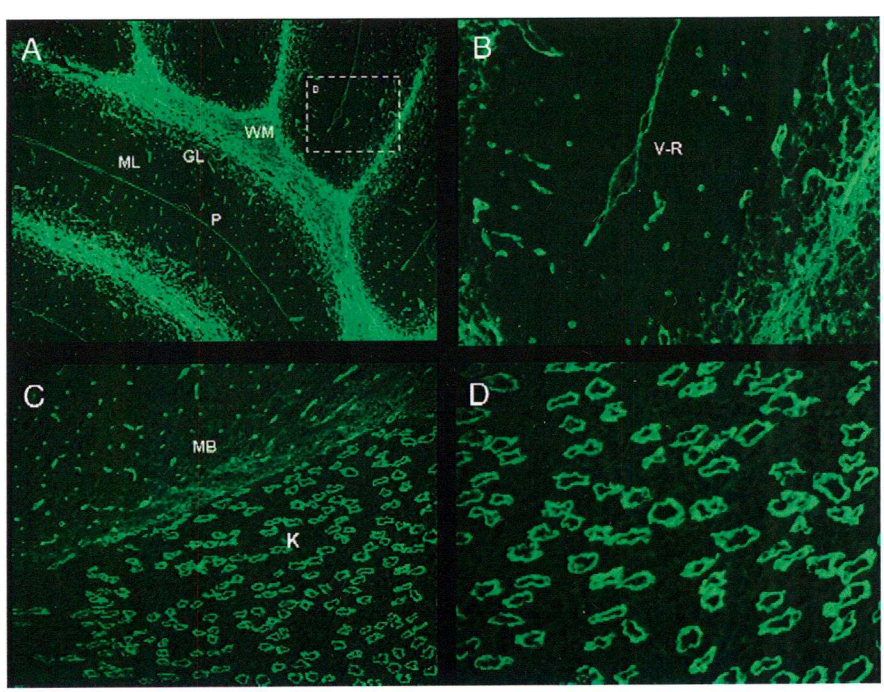

Fig. 3. Immunofluorescence pattern of bound NMO-IgG in mouse CNS and kidney. A (100X): Cerebellar cortex (molecular layer — ML, granular layer — GL, white matter — WM), prominent microvessel and pia (P) staining. B (400X): Detailed picture showing the stained pia outlining a Virchow–Robin space (V–R). C (200×): Midbrain and kidney. D (400×): Kidney, collecting tubules of medulla. (Image Courtesy: Sean J Pittock MD and Vanda A Lennon MD, Departments of Neurology, Laboratory Medicine and Pathology, Neuroimmunology Laboratory, Mayo Clinic, Rochester MN,USA).

Table 2
Aquaporin-4 antibody validation studies

Investigator	Country	NMO/OSMS		LETM		MS	
		n	Positive %	*n*	Positive %	*n*	Positive %
Zuliani (Zuliani et al., 2006)	Spain	10	50	2	100	8	0
Littleton (Littleton et al., 2006)	UK	10	50	2	100	10	0
Kim (Kim, 2006)	Korea	27	19	39	3	25	8
Marignier (Marignier et al., 2006)	France	20	55	11	45	52	9
Jarius (Jarius et al., 2007)	Europe	35	54	5	80	140	3
Akman-Demir (Akman-Demir et al., 2006)	Turkey	14	57	–	–	14	0

Results summarized in the table were presented at ECTRIMS 2006, Madrid. (*n* = number of patients tested; OSMS = optic spinal multiple sclerosis; LETM = longitudinally extensive transverse myelitis; MS = multiple sclerosis; NMO = Neuromyelitis optica).

found only 1 out of 22 patients to be positive and that seropositive patient subsequently developed recurrent LETM (Scott et al., 2006). The ability to predict recurrences of ON or myelitis in patients who present with a single LETM indicates that NMO-IgG serological testing may influence decisions on whom and when to initiate prophylactic immunosuppressive therapy (see treatment section).

A survival analysis of follow-up of 72 patients who presented with two or more sequential events of ON without other clinical manifestations that would support a diagnosis of MS or NMO after the second episode revealed that 12% developed clinically definite NMO and 14% developed MS five years from their first episode of ON (Pirko et al., 2004). While the risk of converting to MS continued to increase beyond five years, conversion to NMO seemed to reach an early plateau. Approximately half the patients at the final follow-up were still classified as having "idiopathic recurrent ON". Of 8 individuals with recurrent ON tested for NMO-IgG prior to 2004, 2 (25%) were seropositive for NMO-IgG (Pirko et al., 2004). This frequency is consistent with our clinical observations that less than 25% of patients with recurrent ON develop NMO.

8.2.2. Atypical cases

Patients with clinically manifest or subclinical (MRI) brain lesions, for whom a reliable diagnosis of NMO was indeterminate or impossible based on the diagnostic criteria proposed in 1999(Wingerchuk et al., 1999) are now suspected to have a NMO spectrum disorder when other clinical characteristics are typical of NMO and when seropositive for NMO-IgG. The absence of symptoms, signs and radiological evidence of brain involvement has traditionally served as a clinical criterion for making the diagnosis of NMO. However, up to 60% patients with longstanding NMO develop lesions, largely nonspecific, and more rarely symptoms referable to brainstem or brain lesions (Nakamura et al., 2005; Pittock et al., 2006a). Among these patients, some with otherwise typical NMO developed brain MRI lesions judged as typical of MS. Approximately 10% of individuals with NMO develop MRI lesions atypical for MS in the brainstem, hypothalamus or large tumefactive lesions in the cerebral hemispheres (Pittock et al., 2006a). NMO-IgG is particularly valuable for assigning the correct diagnosis in such cases.

8.2.3. Patients with significant comorbidities

LETM, ON or both are well reported complications of systemic lupus erythematosus (SLE) or Sjögren's syndrome (SS) (Arabshahi et al., 2006; de Seze et al., 2001; Inslicht et al., 1998; Margaux et al., 1999), although patients described may lack sufficient clinical manifestations to make a formal diagnosis of SLE or SS. We addressed the relationship of myelitis and ON occurring in the context of concomitant connective tissue disease by serological testing for NMO-IgG. Approximately half of such patients are seropositive for NMO-IgG, whereas patients with SLE or SS who do not have manifestations of NMO are uniformly seronegative (Weinshenker et al., 2006b). It is likely that these patients have two coexisting autoimmune disorders rather than a vasculitic complication of a systemic autoimmune disease such as SLE or SS (Pittock et al., 2006b; Weinshenker et al., 2006b), in the same way that NMO may coexist with myasthenia gravis or other systemic autoimmune diseases (Gotkine et al., 2006; Kister et al., 2006).

8.2.4. Asian OSMS

Although clinically similar to NMO, Asian OSMS has traditionally been considered to be separate entity, mainly because of a perceived milder course and the frequent presence of brain lesions. Japanese investigators have attempted to define a "pure form" of OSMS without brain involvement and with long lesions in the cord (Misu et al., 2002). However, the results of the blinded analysis of coded serum samples from Japan strongly supports the identity of Japanese OSMS and NMO to be the same (Lennon et al., 2004). The 58% seropositivity rate in Japanese patients with OSMS (OSMS) did not differ significantly from the 73% seropositivity rate of North American patients with NMO. As mentioned earlier the terms OSMS and NMO do not define exactly the same group of patients (see epidemiology section). Therefore it is possible that some of patients with OSMS had 'western MS', which may explain somewhat lower rates of seropositivity in some Japanese and Asian studies.

8.3. Aquaporin 4

The target antigen of NMO-IgG has been recently identified as the mercurial-insensitive water channel protein, aquaporin-4

(AQP4) which is the dominant water channel within the central nervous system (Lennon et al., 2005).

Aquaporins (AQPs) are a family of widely distributed membrane-inserted water channel proteins providing a pathway for osmotically-driven water transport through cell membranes. CNS AQPs also play a role in osmoreception, K+ siphoning and CSF formation and are strongly implicated in the pathogenesis of cerebral edema following water intoxication or focal cerebral ischemia (Manley et al., 2000; Saadoun et al., 2002; Vajda et al., 2002; Amiry-Moghaddam and Ottersen, 2003; Lehmann et al., 2004).

To determine whether the NMO antigen is restricted to the CNS, NMO-IgG-positive patients' sera was tested by indirect immunofluorescence on sections of normal mouse liver, kidney, and stomach tissues. In contrast to the characteristic intense staining of pial and microvascular elements in the brain (Fig. 3A and B), NMO-IgG did not bind to any vascular or visceral autonomic neural elements in stomach, kidney or liver. However, NMO-IgG bound prominently to distal urine-collecting tubules in the renal medulla (Fig. 3C and D) and to parietal cells in the gastric mucosa. The distribution of NMO-immunoreactivity in CNS, kidney, and gastric mucosa suggested the water channel protein, AQP4, as a candidate antigen. By use of dual immunostaining with AQP4-specific rabbit IgG, confocal microscopy demonstrated that the antigen to which the IgG binds colocalized with AQP4 in all of these tissues.

Using sera from NMO-IgG positive patients and matched controls, in a blinded fashion, on frozen sections of brain tissue obtained from transgenic AQP4 null mice, Lennon et al. showed that IgG from NMO patients' sera bound to microvessels, pia, and subpia in the wild-type brain tissue in a pattern that was identical to that obtained by immunostaining with rabbit anti-AQP4-IgG. However, neither human serum IgG from NMO patients nor the rabbit anti-AQP4-IgG bound detectably to AQP4-null mouse brain tissue (Lennon et al., 2005).

To demonstrate selective binding to membranes of AQP4-transfected cells, stably transfected human embryonic kidney cell line (HEK-293) expressing a transgene encoding full-length AQP4 and plasmid encoded GFP (green fluorescent protein) were created; cells transfected only with the vector served as controls. Coded sera, tested in blinded conditions, showed that neither patient nor controls' IgG bound to the HEK-293 cells that were not transfected with the AQP4-containing vector. However, IgG in the sera of NMO patients stained the plasma membrane of AQP4-transfected cells, consistent with the known expression pattern of AQP4 in cells.

In astrocytic end-feet, AQP4 is closely associated with the cytoskeleton complex, which includes α-syntrophin, β-dystroglycan, and dystrophin (Dp71) (Fig. 4). To exclude a primary effect on one of these cytoskeletal proteins as targets, lysates of the AQP4 and control transfected cell lines were immunoprecipitated with antibodies specific for α-syntrophin, β-dystroglycan,

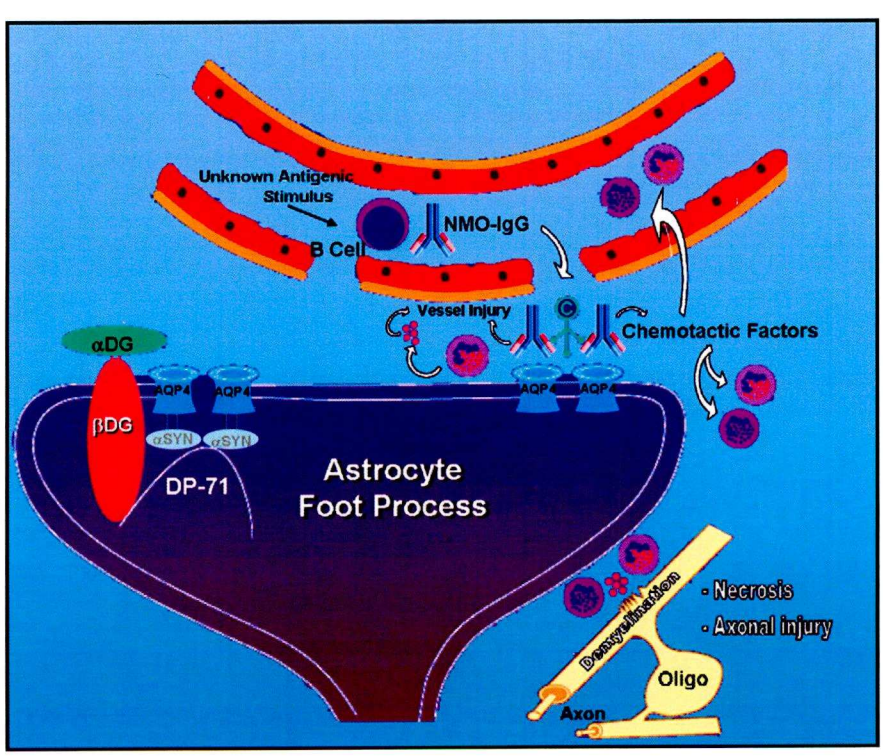

Fig. 4. Proposed pathogenesis of NMO. An unknown antigenic stimulus leads to production of circulating immunoglobulin (NMO-IgG). Though a presumed breach or deficiency in the blood-brain barrier, the antibodies access the extracellular domain of AQP4 at the glia limitans. AQP4 is held in the plasma membrane by a complex of cytoskeletal elements, including α syntrophin (α syn), dystrophin (DP-71), β and α dystroglycan (β DG and αDG). Where a critical density of AQP4 expression is present, complement becomes activated, initiating the inflammatory response. Chemotactic complement fragments and possibly cytokines and chemokines (pink dots) recruit neutrophils and eosinophils. These mechanisms might lead to disruption of the cellular water transport mechanisms and cause demyelination, necrosis and axonal loss, although the mechanisms underlying axonal injury and demyelination remain undefined.

and dystrophin (Dp71) as well as antibodies specific to AQP4. Only NMO-IgG or anti-AQP4 antibodies but not antibodies to other cytoskeletal elements were able to immunoprecipitate the GFP-AQP4 fusion protein.

The mechanism underlying the presumed pathogenicity of AQP4 specific antibodies remains unclear. The antibodies may simply cause disease by binding to their target antigen and activating complement leading to a cascade of inflammation by cytotoxicity, chemotaxis of neutrophils and eosinophils and other complement-mediated mechanisms. Alternatively, they may have a functional effect on the water channel, perhaps disrupting water homeostasis that may lead to direct effects separate from complement activation (Lennon et al., 2005).

8.4. AQP4 immunoreactivity in NMO lesions

Recently, widespread absence of stainable AQP4 in spinal cord tissue of NMO lesions has been demonstrated by several groups (Misu et al., 2006a,b; Roemer et al., 2007; Sinclair et al., 2006). Misu et al. compared aquaporin staining in spinal cord lesions of optico-spinal MS, classical MS and control subjects. In MS plaques, AQP4 staining was increased, presumably reflecting a glial reaction, whereas in NMO lesions, AQP4 was markedly lost. There were some NMO lesions where the myelin basic protein (MBP) stained myelinated fibers were relatively preserved despite the loss of AQP4 staining, suggesting that the loss of AQP4 did not reflect necrosis and cell loss. These findings suggested that AQP4 loss may be the initial event in NMO lesions. The areas surrounding the AQP4-absent NMO lesions had expression of AQP4 and GFAP staining comparable with that in control spinal cords (Misu et al., 2006a,b).

Sinclair et al. have confirmed a lack of expression of AQP4 in optic and spinal cord lesions in a single case of NMO which contrasted sharply with the increased levels of AQP4 expression seen in MS lesions. They also reported immunohistochemical and semi-quantitative analysis of the expression pattern of AQP4 on tissue microarray samples of MS and control white matter. AQP4 was more highly expressed in all categories of MS tissue compared to normal control tissues with the most abundant expression in active lesions (Sinclair et al., 2006).

Lucchinneti et al. (Roemer et al., 2007) have independently demonstrated selective loss of AQP4 immunoreactivity in NMO lesions and performed detailed comparative study with MS. They used carefully matched MS controls, rigorously matching for stage of lesions, and revealed that AQP4 immunoreactivity in MS lesions was variable and dependent on the stage of demyelination. AQP4 immunoreactivity in the periplaque white matter and within reactive astrocytes of active MS lesions was increased, as described by others(Aoki-Yoshino et al., 2005; Misu et al., 2006a; Sinclair et al., 2006). However, AQP4 immunoreactivity was also markedly reduced in inactive MS lesions sampled from both the acute and chronic phases of the disease. Furthermore, these investigators rigorously established that loss of AQP4 immunoreactivity was not attributable to necrosis and cavitation that are common in NMO and are potential confounders.

Lucchinneti et al. also described two pathologic patterns in NMO, both of which were associated with loss of AQP4 immunoreactivity. The first and most prevalent lesion type involved the spinal cord and optic nerves, where AQP4 loss was in the context of vasculocentric immune complex deposition, active demyelination and vascular hyperplasia with hyalinization. These lesions were often cavitary, and involved both gray and white matter in the spinal cord. The second, less frequent lesion type was found in the spinal cord and medulla extending into the area postrema. AQP4 loss was associated with vasculocentric IgG and IgM deposits and complement activation, and tissue rarefaction, but there was no evidence of demyelination (Roemer et al., 2007).

In summary, these findings from 3 different groups all indicate loss of AQP4 in NMO, compared to MS. The intriguing report by Roemer et al. describing loss of AQP4 in the absence of demyelination or necrosis suggests that binding of antibody to AQP4 may be the initial pathogenic event in NMO lesions (Roemer et al., 2007).

9. Pathogenesis

Though the pathogenesis of NMO is incompletely understood, a model may be proposed from recently accumulated observations (Fig. 4). In a susceptible individual, an unknown antigenic stimulus leads to production of circulating immunoglobulin (NMO-IgG). Through a presumed breach or deficiency in the blood-brain barrier, the antibody is able to access the extracellular domain of AQP4 at the glia limitans. Where a critical density of AQP4 expression is present, complement becomes activated, initiating the inflammatory response that ensues. Chemotactic complement fragments may recruit neutrophils and eosinophils, as might cytokines such as IL-17 and IL-8, which have been demonstrated in excess in OSMS (Ishizu et al., 2005). Cross-linking of AQP4 molecules by NMO-IgG may lead to endocytosis and downregulation of the channels, which may limit the inflammatory cascade. These mechanisms might lead to disruption of the cellular water transport mechanisms, which might contribute to some of the lesions that occur in NMO patients. The peripheral synthesis of NMO IgG is consistent with the relative lack of CSF oligoclonal bands in the NMO, as NMO-IgG is not generated primarily by intrathecal synthesis (this in contrast to MS, which is characterized by synthesis of oligoclonal immunoglobulin within the CNS by B cells recruited from periphery). The peripheral source of NMO-IgG may also explain the excellent response to plasma exchange in patients with NMO (Keegan et al., 2002).

The basis of individual susceptibility to NMO remains unexplained, as does the role of cellular limbs of the immune system. Also lacking are definitive proof for the pathogenicity of AQP4 antibodies and details of how tolerance to AQP4 is initially abrogated, assuming that it is the principal antigenic stimulus to the immune system in NMO. The demonstration of AQP4 loss in spinal cord NMO lesions and suggestion that this event occurs even prior to demyelination may point to these as the initial inciting events in the genesis of NMO lesions (Misu et al., 2006a,b; Roemer et al., 2007).

10. Animal models

Lewis rats immunized with medium doses of aggregate myelin oligodendrocyte glycoprotein (MOG) without pertussis toxin develop inflammatory disease confined to the optic nerve and spinal cord characterized by prominent histiocytosis but minimal T cell infiltration (Sakuma et al., 2004). Experimental autoimmune encephalomyelitis (EAE) induced in the Brown Norway (BN) strain of rat by immunization with MOG in Freund's adjuvant also induces an EAE that has a predilection for the optic nerves and spinal cord; active demyelination is associated with prominent deposition of antibody and evidence of complement activation; furthermore, the inflammatory infiltrate contains large numbers of eosinophils, reminiscent of the findings in NMO (Gold and Linington, 2002; Storch et al., 1998).

Recently, two research groups have reported a double-transgenic mouse strain (optic-spinal EAE [OSE] mouse), that spontaneously develops an EAE-like neurological syndrome resembling NMO (Krishnamoorthy et al., 2006; Bettelli et al., 2006; Ransohoff, 2006) by crossing TCR^{MOG} and IgH^{MOG} single-transgenic mice, both on a C57BL/6 background. IgH^{MOG} mice were generated with knock-in technology, inserting the recombined heavy chain of a demyelinating anti-myelin oligodendrocyte glycoprotein (anti-MOG) antibody in the IgJ region. The TCR^{MOG} mice recognized an immunodominant part of MOG. The crossing of these two strains yielded mice in which 20–30% of circulating B cells produced anti-MOG antibodies and expressed a B cell receptor (BCR) that recognized MOG protein. The spontaneously-occurring, inflammatory, demyelinating lesions that developed at about 8 weeks of age in these mice were located in the optic nerve and spinal cord, sparing brain and cerebellum. Single-transgenic litter mates remained healthy. B cells may have presented the antigen (MOG) with MHC class II to the T cells activating them. Activated T cells expressing the proinflammatory cytokines IFN-γ and IL-17 may have facilitated the differentiation of B cells to plasma cells and antibody production. While the authors suggested that this is an experimental model for NMO, the resemblance to NMO in humans maybe superficial (Ransohoff, 2006). The spinal cord lesions in this model are not longitudinally extensive and typically extend only a single vertebral segment. There is also insufficient evidence for humoral contribution to pathology in the lesions; there is no IgG or complement deposition in the tissues. Anti-AQP4 antibodies were also not detected.

Future research into the pathogenesis of NMO would be facilitated by animal models that develop the characteristic vasculocentric lesions in the spinal cord and optic nerves either spontaneously or by passive transfer of AQP4 IgG, or by active immunization with AQP4.

11. Treatment

No clinical trials dedicated to treatment of acute relapses or prevention of relapses have been conducted. Treatment recommendations are largely based on case series or expert opinion (Wingerchuk and Weinshenker, 2005). The first-line therapy for acute attacks is intravenous corticosteroids, typically 1 g of methylprednisolone for five consecutive days, initiated as soon as possible after relapse onset and exclusion or treatment of bacterial infections (e.g. respiratory or urinary tract). Plasmapheresis should be considered when clinical symptoms and signs progress (or severe symptoms fail to improve) despite the corticosteroid infusion. Removal of large molecular weight particles from plasma including autoantibodies, immune complexes and inflammatory mediators is the likely mechanism of action (Lehmann et al., 2006). The favorable effects of plasma exchange in acute CNS demyelinating diseases, including NMO and myelitis of uncertain etiology was demonstrated in a randomized, controlled, crossed-over and double-blind trial. In this study there was improvement in 8 of 19 (42.1%) patients receiving active treatment and only in 1 of 17 (5.9%) receiving sham exchange (Weinshenker et al., 1999). An extended review of the Mayo Clinic experience with plasma exchange for acute CNS demyelinating disease showed that, 6 of 10 (60%) patients with acute attacks of NMO recovered moderately or markedly after the plasma exchange treatment (Keegan et al., 2002). The efficacy of plasma exchange was also retrospectively studied in MS patients who had a fulminant attack and were submitted to a diagnostic brain biopsy. When considering the four different immunopathological patterns of demyelination seen in early MS lesions, only the patients classified as pattern II with antibody/complement-associated process had a neurological improvement (Keegan et al., 2005). By analogy, this may explain the apparently superior responsiveness of attacks of NMO, because of the prominent IgG deposition and evidence of complement activation.

Treatments aiming at relapse prevention should be initiated as soon as the diagnosis of a relapsing NMO is made. It is also reasonable to start therapy after a first episode of LETM in patients seropositive for NMO-IgG, since NMO-IgG has proven to be a potent predictor of future relapse in this context (Weinshenker et al., 2006a). Immunosuppression, rather than interferon beta or glatiramer acetate, which are used for prototypic MS, is the preferred treatment (Papeix et al., 2005). Azathioprine (2.5–3 mg/kg daily) has been the most frequently used drug, often in combination with prednisone (1 mg/kg daily or every other day), either temporarily until azathioprine has taken full effect, or indefinitely in patients who relapse following gradual withdrawal of steroids. Mandler et al. studied 7 patients with NMO treated with azathioprine (75–100 mg) and prednisone 10 mg over 18 months. These patients remained relapse free for 18 months and had improved disability(Mandler et al., 1998).

Mycophenolate mofetil (1–3 g/day), which has a cytostatic effect on T and B lymphocytes and suppresses antibody formation, may achieve faster immunosuppression. A case of sustained remission for 2 years with mycophenolate 2 g/day has been reported (Falcini et al., 2006).

Monthly intravenous infusions of mitoxantrone hydrochloride in 5 patients over 2 years, (12 mg/m^2, for 6 months followed by 3 additional treatments every 3 months) appeared to reduce relapse rates in four out of the five patients with relapsing NMO (Weinstock-Guttman et al., 2006).

Monthly intravenous infusions of immunoglobulin were effective in 2 patients. The first patient was followed up for 5 and half years and the second for one year without relapses

(Bakker and Metz, 2004; Weinstock-Guttman et al., 2006; Minagar, 2002).

Although interferon beta was reported to reduce attacks in Japanese OSMS, the study did not show statistically significant differences between low and high dose interferon beta-1b-treated patients, possibly due to lack of power; the MRI analysis was non informative in this subgroup of patients who generally have no or few MRI lesions in the brain and accordingly, we do not consider these results as definitive(Saida, 2006; Saida et al., 2005). In fact, one Japanese series has suggested that interferon beta may worsen NMO (Warabi et al., 2007).

Cree et al. conducted an open-label study of rituximab (a murine/human chimeric monoclonal antibody that targets CD20+ B cells) in eight NMO patients who had failed other therapeutic regimens with a mean follow up of 1 year. Each patient received four infusions of IV rituximab dosed at 375 mg/m^2, administered once per week. B cell counts were followed bimonthly by FACS using the CD19 marker. When B cell counts became detectable, patients were given the option to be retreated with rituximab. Rituximab retreatment consisted of two IV infusions of 1000 mg administered 2 weeks apart. The drug was well tolerated. Six patients were relapse free over 12 months and seven had a neurological improvement(Cree et al., 2005). Re-treatments seem feasible without major cumulative toxicity Because of its selective action against B cells, rituximab treatment may be an effective therapeutic option in NMO. However, the potential risks of opportunistic infections and malignancies must be considered and, perhaps, are not yet fully appreciated.

The optimal duration of treatment in patients without further relapses with immunosuppressants is uncertain. The long term side effects of medications have to be weighed against the potential risk of relapses. Whether NMO-IgG titers could guide therapy is uncertain and appropriate studies are being pursued.

12. Conclusion

Although NMO was described more than a century ago, there were few advances in understanding of the disease until recently. Over the past decade, there has been a resurgence of interest in this frequently disabling, occasionally life-threatening, but treatable disease. Elucidating the pathogenesis of NMO may offer important insights into the pathobiology of MS and other demyelinating disorders. Passive or active transfer of the disease, development of animal models, identification of potential genetic and environmental susceptibility factors are ongoing arenas of research. Discovery of a potential specific antigenic target, AQP4, may facilitate the development of effective antigen-specific therapy.

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ORIGINAL CONTRIBUTION

Treatment of Neuromyelitis Optica With Rituximab

ARCHIVES EXPRESS

Retrospective Analysis of 25 Patients

Anu Jacob, MD, MRCP, DM; Brian G. Weinshenker, MD; Ivo Violich, BS; Nancy McLinskey, MD; Lauren Krupp, MD; Robert J. Fox, MD; Dean M. Wingerchuk, MD; Mike Boggild, MD, MRCP; Cris S. Constantinescu, PhD; Aaron Miller, MD; Tracy De Angelis, MD; Marcelo Matiello, MD; Bruce A. C. Cree, MD, PhD, MCR

Background: Neuromyelitis optica (NMO) is an uncommon, life-threatening inflammatory demyelinating disorder. Recently, much has become known about its immunopathogenesis. However, optimal treatments, with expected outcomes, have not been established.

Objective: To evaluate the use and efficacy of rituximab for treating NMO.

Design: Retrospective multicenter case series of NMO patients treated with rituximab.

Setting: Seven tertiary medical centers in the United States and England.

Patients: Twenty-five patients (including 2 children), 23 of whom experienced relapses despite use of other drugs before rituximab. Extended follow-up of 7 previously reported patients is included.

Interventions: Infusions of rituximab at median intervals of 8 months.

Main Outcome Measures: Annualized relapse rate and disability (expressed as Expanded Disability Status Scale score).

Results: At a median follow-up of 19 months, the median annualized posttreatment relapse rate was lower than the pretreatment rate (0 [range 0-3.2] vs 1.7 [range, 0.5-5] relapses, $P < .001$). Disability improved or stabilized in 20 of 25 patients (80%, $P = .02$). Two patients died during the follow-up period, 1 owing to a brainstem relapse and 1 owing to suspected septicemia. Infections were reported in 20% of patients.

Conclusions: In NMO, treatment with rituximab appears to reduce the frequency of attacks, with subsequent stabilization or improvement in disability.

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NEUROMYELITIS OPTICA (NMO) is an inflammatory demyelinating disorder, usually relapsing, that targets the optic nerves and spinal cord, resulting in attack-related accrual of disability. It is probably the same disorder as Asian opticospinal multiple sclerosis in those whose spinal cord lesions extend 3 or more segments during acute attacks. Compared with typical multiple sclerosis, NMO is more rapidly disabling; 50% of patients must use a wheelchair and 62% become functionally blind (visual acuity of 20/200 or worse) at 5 years.[1] Treatment of NMO with interferon beta appears to be substantially less effective than immunosuppressive therapy[2] and possibly even deleterious,[3] which further underscores the difference between NMO and typical multiple sclerosis. Randomized controlled trials have not been conducted on NMO, and treatment options are based on small case series that used immunosuppressant medications, including azathioprine,[4] mitoxantrone,[5] and mycophenolate mofetil.[6] Despite use of these drugs, patients with NMO often experience ongoing disease activity. Open label use of rituximab (Rituxan; Biogen Idec, Cambridge Massachusetts/Genentech, San Francisco, California), a monoclonal antibody against $CD20^+$ B cells, was reported to be potentially beneficial in patients who are refractory to a variety of immunotherapies.[7,8] Given the lack of proven efficacious treatments, this case series led us to use rituximab in patients with NMO, even as a first-line treatment. We describe our multicenter, longitudinal experience of the effectiveness and adverse effects of rituximab in 25 cases of NMO.

METHODS

This is a retrospective case series of the use of rituximab in NMO. Investigators from 20 centers who attended an exploratory meeting about a potential clinical trial of a new humanized monoclonal antibody that, like rituximab, recognizes the CD20 protein were approached to participate in this study. Seven centers responded to the request. Investigators recalled and contributed information on all the patients to whom rituximab was administered for NMO (University of California–San Francisco, San Francisco [n=7]; Stony Brook Hospital, Stony Brook, New York [n=6]; Mayo Clinic, Rochester, Minnesota [n=5]; Mayo Clinic, Scottsdale, Arizona [n=2]; The Walton Center, Liverpool, England [n=2]; Mellen Center, Cleveland Clinic, Cleveland, Ohio [n=2]; and Mount Sinai Hospital, New York, New York [n=1]). University of California–San Francisco provided extended follow-up on 7 previously reported patients.[7] New patients from University of California–San Francisco were not included because of contemporaneous recruitment of patients with NMO into a clinical trial. Local institutional review board approval was obtained at each center and informed consent was obtained from patients or their next of kin. All patients with relapsing NMO or longitudinally extensive transverse myelitis[9] who were treated with at least 1 dose of rituximab and who had at least 6 months of follow-up were included. Patients who did not meet these criteria were excluded. Given the small number of patients treated at each center, we are reasonably confident, but not absolutely certain, that other eligible patients were not excluded. Completed case report forms were analyzed at the Mayo Clinic in Rochester. All patients who were reported to the analysis team by the treating hospitals were found to be eligible and were included. Statistical analysis was performed using JMP, version 6.0 (SAS, Cary, North Carolina).

RESULTS

PATIENT CHARACTERISTICS

All 25 patients qualified for inclusion in the study, according to the inclusion and exclusion criteria. There were 3 men, 20 women, and 2 girls. The median age of the patients was 38 years (range, 7-65 years). Two children received their initial rituximab treatment at age 7 years (patient 8) and 14 years (patient 11). Twenty-three patients had NMO and 2 had NMO-IgG–seropositive recurrent longitudinally extensive transverse myelitis. The median interval from onset of NMO to treatment with rituximab was 4.5 years (range, 0.8-17 years). The clinical and demographic profiles of the patients are outlined in the **Table**. Seventy percent of patients assessed were positive for NMO-IgG (14 of 20 patients). Seven of 8 patients from the previously reported case series were included.[7] One patient from the initial study was lost to follow-up despite multiple attempts to contact her. Rituximab was used in 23 patients owing to failure of other medications. In 19 patients, more than 1 treatment was used before treatment with rituximab. Rituximab was used as a first-line therapy in 2 patients.

TREATMENT WITH RITUXIMAB

Two rituximab regimens were used: (1) 375 mg/m^2 infused once per week for 4 weeks (n=18)[10] and (2) 1000 mg infused twice, with a 2-week interval between the infusions (n=4).[11] These regimens were based on rituximab's use in rheumatology,[11] hematology,[10] and the previously reported series of patients with NMO.[7] Local practice determined selection of the regimen. The specific treatment regimen for the remaining 3 patients was not available.

Seventeen patients were retreated with rituximab: 8 had 4 additional doses of 375 mg/m^2 and 7 had 2 1000- mg doses 2 weeks apart. Data regarding the subsequent dosing regimen were unavailable for 2 patients. Other immunotherapies with rituximab were used in 5 patients: azathioprine with prednisone (n=1), prednisone (n=3), and interferon beta (n=1).

The median interval between the last relapse and start of treatment was 1 month (range, 0-7 months; mean, 1.5 months). Twenty of the 25 patients received treatment within 2 months of their last relapse. The median interval between rituximab treatments was 8 months (range, 4-26 months). Subsequent treatments were either planned at 6- to 12-month intervals or were administered after relapse or when CD19$^+$ B cells became detectable. Counts of CD19 cell markers were not routinely monitored in all patients, and a threshold value was not used to determine the timing of retreatment.

FOLLOW-UP

The median follow-up interval after initial rituximab treatment was 19 months (range, 6-40 months). Eighteen patients planned to continue treatment with rituximab at their last follow-up and 15 received rituximab during the preceding 6 months of follow-up.

Seven patients discontinued treatment. The reasons for discontinuation were death (n=2 [patients 5 and 10]), relapses (n=2 [patients 18 and 22]), pregnancy (n=1 [patient 14]), and other (n=2 [patients 13 and 20]).

After experiencing relapses after treatment with rituximab, 2 patients started other treatments (patients 18 and 22). Patient 18 required plasmapheresis every 6 weeks in conjunction with pulsed intravenous corticosteroids twice per month and mycophenolate mofetil to maintain remission from additional relapses. Patient 22 started treatment with cyclophosphamide after her third relapse.

Patient 20, who took azathioprine throughout the study, was averse to parenteral administration of drugs and wished to restart treatment with azathioprine. After 2 minor relapses, the dose of azathioprine was increased; the patient was relapse-free when this manuscript was written. One patient had a planned pregnancy (patient 14) and discontinued treatment. Patient 13 discontinued treatment with rituximab and did not receive other immunosuppressive treatment despite having a minor relapse (**Figure**). However, after completion of this analysis, she was readmitted with a severe spinal cord relapse 2 years after her last infusion of rituximab (not shown in the Figure) and has now resumed taking rituximab; this relapse was not included in the analysis of the relapse rate.

Table. Clinical Profile of Patients Treated With Rituximab

Patient No./Sex/Age at First Rituximab Treatment, y	Diagnosis	Disease Duration at First Rituximab Treatment, mo	NMO-IgG Status	LETM on MRI	Drugs Used Before Rituximab (Duration of Treatment, mo)	Concomitant Immunotherapy
1/F/49	NMO	4.84	–	+	Glatiramer acetate (7)	
2/M/28	NMO	5.25	+	+	Interferon beta (24) Azathioprine (28) Intravenous immunoglobulins (23)	
3/F/19	NMO	4.62	+	+	Azathioprine (9) Interferon beta (7)	
4/F/43	NMO	2.09	–	+	None	
5/F/43	NMO	17.22	Test not done	+	Azathioprine (U) Prednisone (U) Mitoxantrone (2) Cyclophosphamide (U) Mycophenolate mofetil (U)	
6/M/22	NMO	15.79	+	+	Azathioprine(U) Prednisone (U) Methotrexate (U)	
7/F/40	NMO	6.77	Test not done	+	Glatiramer acetate (9) Azathioprine (13) Interferon beta (3) Mitoxantrone (2) Azathioprine (20) Prednisone (20)	Azathioprine
8/F/7	NMO	4.17	+	–	Prednisone (3)	
9/F/21	NMO	7.92	+	+	Interferon beta (6) Azathioprine (27) Cyclophosphamide (1) Mitoxantrone (2)	
10/F/53	NMO	3.68	+	+	Mitoxantrone (5) Azathioprine (6)	
11/F/14	NMO	7.25	–	U	Prednisone (7) Intravenous immunoglobulins (U)	Prednisone, azathioprine
12/F/50	NMO	0.83	Test not done	+	U	
13/F/33	NMO	2.89	+	+	Interferon beta (U) Intravenous immunoglobulins (U)	
14/F/28	NMO	6.08	Test not done	+	Interferon beta (60) Azathioprine (72) Prednisone (24) Intravenous immunoglobulins (15)	
15/F/18	NMO	8.17	+	+	Interferon beta (102) Mitoxantrone (3) Intravenous immunoglobulins (4)	Interferon beta
16/F/19	NMO	6.32	+	+	Interferon beta (12) Glatiramer acetate (3) Interferon beta (45) Intravenous immunoglobulins (7) Mitoxantrone (3)	
17/F/22	NMO	7	+	+	Interferon beta (12) Azathioprine (14) Mitoxantrone (22) Azathioprine (4)	
18/F/52	NMO	4.25	–	+	Interferon beta (26)	
19/F/54	NMO	1.17	+	+	Azathioprine (5) Prednisone (5)	Prednisone
20/F/43	Relapsing myelitis	4.13	+	+	Hydroxychloroquine (1) Azathioprine (53) Prednisone (12)	Prednisone
21/F/43	Relapsing myelitis	2.62	+	+	Cyclophosphamide (22)	
22/F/35	NMO	3.63	–	+	Glatiramer acetate (24)	
23/F/47	NMO	3.1	+	+	Prednisone (3) Azathioprine (6)	
24/M/62	NMO	2.88	Test not done	+	Interferon beta (4) Azathioprine (2)	
25/F/24	NMO	4.93	–	+	Azathioprine (12) Prednisone (12) Interferon beta (33) Intravenous immunoglobulins (1)	

Abbreviations: LETM, longitudinally extensive transverse myelitis; MRI, magnetic resonance imaging; NMO, neuromyelitis optica; U, unknown; +, positive; –, negative.

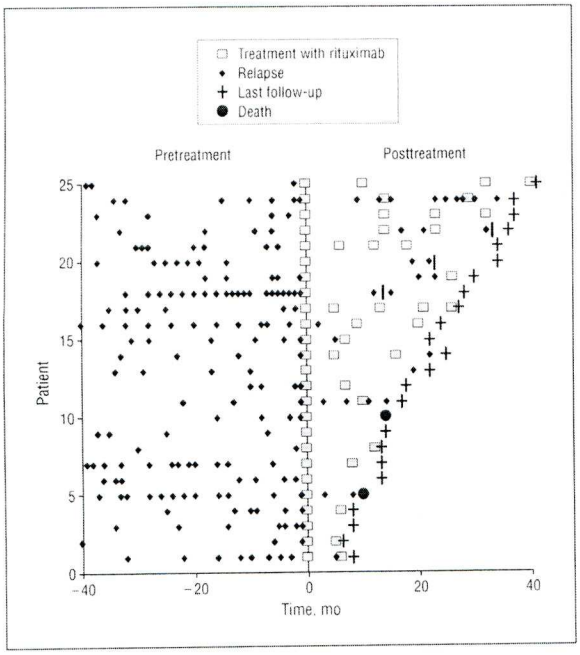

Figure. Relapses in patients with neuromyelitis optica before and after treatment with rituximab.

TREATMENT EFFICACY

Relapse Rates

Relapses before and after treatment are represented in the Figure. All relapses after onset of rituximab treatment were considered. However, if new treatments were started, only relapses until the start date of the new treatment were included (patients 18, 20, and 22). Relapses in patients who stopped taking rituximab but who were not undergoing any other treatments were included. For all 25 patients, the median annualized pretreatment relapse rate was 1.7 relapses (range, 0.5-5 relapses) and the median annualized posttreatment rate was 0 relapses (range, 0-3.2 relapses, $P < .001$, Wilcoxon signed-rank test) at a median follow-up of 19 months. The following sensitivity analyses were performed to address whether these results were biased by including patients who died, were followed up for less than 1 year after treatment with rituximab, or received concomitant treatment with other immunotherapies. If the 2 patients who died (patients 5 and 10) were excluded (n = 23), the median pretreatment annualized relapse rate was 1.7 relapses (range, 0.6-4.9 relapses) and the posttreatment was 0 relapses (range, 0-3.2 relapses) ($P < .001$). If the 5 patients who were undergoing additional immunotherapies (patients 7, 11, 15, 19, and 20) and the 2 who died were excluded (n = 18), the median pretreatment relapse rate was 1.7 (range, 0.7-4.9) and the median posttreatment relapse rate was 0 (range, 0-2.9) at a median follow-up of 18 months. If the patients who were followed up for less than 1 year were also excluded (patients 1, 2, 3, and 4) along with those taking additional immunotherapies (n = 5) and those who died (n = 2), the median pretreatment and posttreatment relapse rates were 1.5 (range, 0.7-4.9) and 0 (range, 0-2.9), respectively, at a median follow-up of 22 months in the remaining 14 patients.

Disability

Two patients died (patients 5 and 10). The median Expanded Disability Status Scale (EDSS) score at the start of treatment with rituximab (n = 25) was 7 (range, 3-9.5) and at last follow-up at a median of 19 months was 5 (range, 3-10) ($P = .02$). The EDSS scores stabilized in 9 patients and improved in 11. In 5 patients (patients 3, 5, 10, 13, and 20), EDSS scores worsened.

ADVERSE EVENTS OBSERVED DURING TREATMENT AND FOLLOW-UP

Transient infusion-related adverse effects occurred in 7 of 25 patients (28%) and were not dose-limiting. New or reactivated infections developed in 5 of 25 patients (20%) and included herpes simplex (cold sore) and positive tuberculin skin test (n = 1), herpes zoster (n = 1), recurrent *Clostridium difficile* colitis (n = 1), a cutaneous fungal infection (n = 1), and fatal urinary tract–related septicemia (n = 1). Worsening of preexisting seborrheic dermatitis occurred in 1 patient.

DEATHS

Patient 5 developed recurrent *C difficile* colitis after her first rituximab infusion followed by a urinary tract infection. She died 9 months after the last dose following a severe relapse; she had a brainstem lesion that extended into the hypothalamus and thalamus on magnetic resonance imaging. Clinical manifestations were lethargy, obtundation, electrolyte imbalance, and hypothermia. $CD19^+$ B cells were not detectable 2 months before her death (7 months after last infusion).

Patient 10 died 6 months after the last dose of rituximab. She was obtunded and suspected of being septic. An autopsy of the brain and spinal cord showed confluent demyelination from the lumbar spinal cord to the cervical cord with necrosis and cavitation, perivascular lymphoid infiltrate, and macrophage infiltrates. Both optic nerves were atrophic and had lymphocyte and macrophage infiltrates. The brain did not show any pathology. $CD19^+$ B cells were undetectable 5 months after her last infusion (1 month before death). Her total lymphocyte count was 900/μL (to convert to $\times 10^9$ per liter, multiply by 0.001) before death (normal, 900-2900/μL) compared with 2730/μL before starting rituximab. She also had low IgA, IgG, and IgM concentrations 1 month before her death. She was treated with mitoxantrone before initiation of rituximab.

COMMENT

Neuromyelitis optica is a relapsing disorder with rapid accrual of attack-related disability and a high, early mortality rate.[1] Controlled trials of treatments to prevent relapses are unavailable, and treatment is based on case series and expert opinion. Although 2 cases were reported to enter remission with the use of glatiramer acetate,[12,13] im-

munomodulatory medications (interferon beta or glatiramer acetate) do not appear to be beneficial in larger case series.[2,3] Immunosuppressive drugs are the mainstay of treatment of NMO. Azathioprine[4] is the most widely used medication. Cyclophosphamide, mitoxantrone,[5] cyclosporine, methotrexate, and mycophenolate mofetil[6] have also been used.[1,4] However, patients commonly relapse on these treatments; relapses with brainstem or cervical cord involvement are a frequent cause of death in NMO.[1]

In this retrospective, multicenter case series, we evaluated the use of rituximab in patients with NMO who were largely refractory to other treatments. Relapse rates improved and disability stabilized or improved in 20 of 25 patients (80%), a rate that is similar to previously reported observations.[7]

Although the infections cannot be definitively classified as opportunistic, the death of 1 patient owing to sepsis and the occurrence of infections in others raise important concerns about rituximab's safety in this specific disease setting. Patient 10 died following a presumed urinary tract infection and had reduced lymphocyte counts and immunoglobulin concentrations. It is possible that treatment with rituximab and/or prior treatment with mitoxantrone contributed to this patient's sepsis.

We did not attempt to identify predictive factors of a beneficial response to rituximab treatment. The small size of the study, retrospective acquisition of data, and positive treatment response in 80% of patients precludes such an analysis. We did not compare the 2 regimens owing to the differing number of patients in the 2 groups and the switching between the 2 regimens for subsequent treatments in some patients.

It is unclear whether rituximab should be the first treatment for NMO. Comparative studies of the immunosuppressive treatments used for NMO have not been undertaken. Most patients in this series are from a selected population with treatment-refractory NMO. It is possible that patients who have never undergone treatment may benefit from more widely available and less expensive immunosuppressive medications. Furthermore, even in this small group, there are apparent rituximab treatment failures, demonstrating that it is not effective in all patients. A recent case report of 2 patients with variable responses to rituximab highlights this point.[8]

Safety concerns regarding rituximab persist. The relative risk of infections with rituximab vs other immunosuppressive treatments of NMO is unknown. Recent reports of progressive multifocal leukoencephalopathy in 2 patients with systemic lupus erythematosus, 1 patient with systemic vasculitis, and 23 patients with lymphoma treated with rituximab are concerning.[15] However, these patients received treatment with other immunosuppressive medications, either sequentially or combined with rituximab. Lymphomas and systemic lupus erythematosus are thought to predispose individuals to progressive multifocal leukoencephalopathy, irrespective of treatment. Progressive multifocal leukoencephalopathy has also been associated with azathioprine,[16,17] cyclosporine,[18,19] cyclophosphamide,[20] and mycophenolate mofetil.[21]

Rituximab treatment is more expensive[22] than generic immunosuppressive drugs, such as azathioprine. However, the higher cost may offset the cost of hospitalizations for relapses and plasma exchanges if rituximab is more effective.

Our study is limited by the retrospective nature of the case series, which is based on the clinical experience with rituximab at 7 centers, and several important caveats should be mentioned. First, 2 treatment regimens were used, though the total dose administered to each patient was similar. Second, the intervals between courses of treatment varied. Third, it is possible that regression to the mean contributed to the decline in relapse rates. However, we believe that this is unlikely because there was no specific relapse requirement preceding rituximab treatment for inclusion in this case series and because the pretreatment relapse rates were determined from disease onset rather than from a fixed period immediately preceding rituximab therapy. Fourth, the interval between rituximab and previous drugs was often short, and it is possible that some of the effects that were attributed to rituximab could be due to residual benefits from other medications. Fifth, rituximab was used with other drugs in 5 patients. Sixth, $CD19^+$ B-lymphocyte counts were not measured to assess efficacy of treatment and timing of retreatment. Lastly, the pretreatment EDSS score may have been determined immediately postrelapse, while the last available EDSS score may have been determined during a period of stability, thus showing improvement attributable to recovery from an attack.

Despite these limitations, we feel that the data are credible, particularly considering the robust suppression of disease activity in patients with NMO following rituximab treatment. Recently, much has been learned about the pathogenesis of NMO.[23] However, data on treatment of NMO are sparse, and randomized, controlled trials on this disease have never been performed. This is the largest case series of a single drug treatment, particularly in the subgroup of patients with NMO who are refractory to conventional treatment in whom the risk of mortality is high. Controlled trials are difficult to organize owing to a variety of reasons, including the rarity of the disease, need for early treatment, and high morbidity from relapses. Given the absence of such controlled trials, studies such as this provide at least anecdotal evidence to help guide clinicians in selecting treatments for this potentially life-threatening disease.

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Author Contributions: Dr Jacob had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Jacob, Weinshenker, Fox, and Cree. *Acquisition of data:* Jacob, Weinshenker, Violich, McLinskey, Krupp, Fox, Wingerchuk, Boggild, Constantinescu, Miller, De Angelis, Matiello, and Cree. *Analysis and interpretation of data:* Jacob, McLinskey, Boggild, Constantinescu, and Cree. *Drafting of the manuscript:* Jacob, Violich, Boggild, and Cree. *Critical revision*

of the manuscript for important intellectual content: Jacob, Weinshenker, McLinskey, Krupp, Fox, Wingerchuk, Boggild, Constantinescu, Miller, De Angelis, Matiello, and Cree. *Statistical analysis:* Jacob and Cree. *Obtained funding:* Boggild and Cree. *Administrative, technical, and material support:* Jacob, Violich, McLinskey, Fox, Matiello, and Cree. *Study supervision:* Weinshenker, Krupp, Boggild, and Cree.

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ORIGINAL CONTRIBUTION

Treatment of Neuromyelitis Optica With Mycophenolate Mofetil

Retrospective Analysis of 24 Patients

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Background: Neuromyelitis optica (NMO) is the first inflammatory autoimmune demyelinating disease of the central nervous system for which a specific antigenic target has been identified: the marker autoantibody NMO-IgG specifically recognizes the astrocytic water channel aquaporin 4. Current evidence strongly suggests that NMO-IgG may be pathogenic. Since disability accrues incrementally related to attacks, attack prevention with immunosuppressive therapy is the mainstay of preventing disability.

Objective: To evaluate the efficacy and safety of mycophenolate mofetil therapy in NMO spectrum disorders.

Design: Retrospective case series with prospective telephone follow-up.

Setting: Mayo Clinic Health System.

Patients: Twenty-four patients with NMO spectrum disorders (7 treatment-naive).

Intervention: Mycophenolate mofetil (median dose of 2000 mg per day).

Main Outcome Measures: Annualized relapse rates and disability (Expanded Disability Status Scale).

Results: At a median follow-up of 28 months (range, 18-89 months), 19 patients (79%) were continuing treatment. The median duration of treatment was 27 months (range, 1-89 months). The median annualized posttreatment relapse rate was lower than the pretreatment rate (0.09; range, 0-1.5; and 1.3; range, 0.23-11.8, respectively; $P < .001$). Disability stabilized or decreased in 22 of 24 patients (91%). One patient died of disease complications during follow-up. Six patients (25%) noted adverse effects during treatment with mycophenolate.

Conclusion: Mycophenolate is associated with reduction in relapse frequency and stable or reduced disability in patients with NMO spectrum disorders.

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NEUROMYELITIS OPTICA (NMO) is an idiopathic autoimmune inflammatory demyelinating disorder that affects the central nervous system with a predilection for the optic nerve and spinal cord. It is the first inflammatory autoimmune demyelinating disease of the central nervous system for which a specific antigenic target, the astrocytic water channel aquaporin 4, has been identified.[1,2] Neuromyelitis optica–IgG is an autoantibody specific for this water channel and is a clinically validated serum biomarker that distinguishes relapsing NMO from multiple sclerosis, which has no distinguishing biomarker.[3] Patients seropositive for NMO-IgG with either optic neuritis or longitudinally extensive transverse myelitis are considered to have limited forms of NMO, which we have called NMO spectrum disorders. Seropositivity for NMO-IgG in these disorders is predictive of further relapses.[4,5]

Disability in NMO accrues incrementally in relationship to attacks.[6,7] Fifty percent of patients are dependent on a wheelchair and 62% are functionally blind at 5 years.[6,7] In contrast, patients with multiple sclerosis have a more favorable outcome, and disability usually occurs during the progressive rather than the relapsing phase of their disease.[8-10] Because disability in NMO is attack-related, attack prevention is anticipated to be an effective strategy in prevention of cumulative disability. Immunosuppressive therapy is the mainstay of preventing attacks and thus disability.[11] Azathioprine,[12] corticosteroids,[13] mitoxantrone,[14] and more recently rituximab[15,16] have been reported to be effective in small case series. No randomized controlled trials have been conducted in this disorder.

Recently, mycophenolate mofetil has been increasingly used in NMO, though to date only 1 case of NMO treated with mycophenolate mofetil has been reported.[17] Mycophenolate mofetil (Cellcept, F. Hoffmann-La Roche, Basel, Switzerland) is a 2-morpholinoethyl ester of mycophenolic acid and a reversible inhibitor of inosine monophosphate dehydrogenase that is involved in guanosine nucleotide synthesis, on which the T and B lymphocytes are exclusively dependent for proliferation.[18] It also exerts an inhibitory effect on antibody synthesis. It is routinely used in cardiac and renal transplant settings and is being increasingly used as a treatment option in a variety of other autoimmune conditions, including systemic lupus erythematosus–induced and other immune nephropathies, autoimmune hepatitis, psoriasis, blistering dermopathies, and vasculitides. It is also used to treat myasthenia gravis,[19] multifocal motor neuropathy,[20] inflammatory myopathies,[21] chronic inflammatory demyelinating polyradiculoneuropathy,[22] autonomic ganglionopathy,[23] vasculitic neuropathies,[24] and multiple sclerosis.[25-27] It is considered to have fewer adverse effects than other immunosuppressive agents and is administered orally. The optimal dose and duration and the effect size of mycophenolate mofetil for prevention of NMO attacks remain uncertain. Herein we report on our experience with mycophenolate mofetil in a cohort of adult patients with NMO.

METHODS

We performed a retrospective medical record review of all Mayo Clinic patients with NMO (per 2006 diagnostic criteria) or an NMO spectrum disorder (NMO-IgG–seropositive patients with optic neuritis or longitudinally extensive transverse myelitis) who were treated with mycophenolate mofetil anytime from June 1999 until June 2006. Patients were identified by searching the centralized medical records of all the 3 Mayo Clinic sites (Rochester, Minnesota; Scottsdale, Arizona; and Jacksonville, Florida) using the search terms *neuromyelitis optica*, *Devic's disease*, *optic neuritis*, or *myelitis* and *mycophenolate* or *Cellcept*.

Local institutional review board approval was secured and informed consent obtained from patients or next of kin. Telephone follow-up was performed by one of us (A.J., M.M., or S.J.P.) in 2008. Data analysis was performed at the Mayo Clinic, Rochester, using JMP, version 6.0 (SAS Institute Inc, Cary, North Carolina). Wilcoxon signed-rank test was used to compare pretreatment and posttreatment relapse rates and Expanded Disability Status Scale (EDSS) scores. Relapses and disability were assessed by medical record review and telephone interview. A relapse was defined as objective worsening of neurologic function lasting more than 24 hours.

RESULTS

PATIENT CHARACTERISTICS

Twenty-four patients (19 women) were identified. The median age of the patients at onset of treatment with mycophenolate mofetil was 56 years (range, 34-77 years). The median duration of NMO to onset of treatment with mycophenolate mofetil was 4.2 years (range, 0.1-39 years). The diagnosis was NMO in 15 patients (63%; 13 of 14 tested were NMO-IgG–seropositive and all fulfilled 2006 NMO diagnostic criteria); relapsing longitudinally extensive transverse myelitis in 7 patients (29%); relapsing optic neuritis in 1 patient (4%); and a single episode of longitudinally extensive transverse myelitis in 1 patient (4%). The patients with relapsing or single episodes of longitudinally extensive transverse myelitis or relapsing optic neuritis were all NMO-IgG–seropositive.

TREATMENT WITH MYCOPHENOLATE MOFETIL

Seven patients (29%) were treatment-naive. The remaining 17 patients (71%) had previously used other immunosuppressive (n=6), immunomodulatory (n=2), or combination (n=9) therapy. Twelve (50%) received azathioprine (**Table**). Reasons for switching to mycophenolate mofetil included medication adverse effects (n=7 [29%]), continued relapses (n=8 [33%]), and contraindication to azathioprine owing to low thiopurine methyltransferase levels (n=2 [8%]). The median dose of mycophenolate mofetil used was 2000 mg per day (range, 750-3000 mg per day). The clinical and demographic profiles of the patients are summarized in the Table.

FOLLOW-UP

After identification of the initial cohort in June 2007, telephone follow-up and medical record review were again performed in 20 patients in late 2008 at a median of 27 months after starting treatment (range, 18-89 months). Telephone contact was not possible for 4 patients (1 died); medical record review in these patients provided posttreatment follow-up data for a median of 46 months (range, 21-54 months). The median follow-up of all patients (irrespective of whether they continued treatment) was 28 months (range, 18-89 months).

The median duration of treatment with mycophenolate mofetil was also 27.4 months (range, 1-89 months). At last review, 19 patients (79%) continued treatment with mycophenolate mofetil, with a median duration of 29.4 months (range, 20-89 months). Five patients (21%) discontinued taking the drug after a median interval of 16 months (range, 1-54 months). The reasons for discontinuation were death in 1 (patient 21), relapses in 2 (patient 3 switched to rituximab at 3 months, patient 14 to azathioprine at 25 months), and adverse effects in 1 (patient 24 had low white blood cell counts and switched to azathioprine at 1 month). Patient 1 had neither relapses nor adverse effects but chose to switch to rituximab after 1 month of mycophenolate mofetil.

TREATMENT EFFICACY

Relapse Rates

The **Figure** depicts the timing of relapses before and after treatment. All relapses after initiation of mycophenolate mofetil until its discontinuation or until the last date of follow-up were included in the analysis. Nine pa-

Table. Clinical Characteristics of Patients Treated With Mycophenolate Mofetil

Patient No./ Sex	Diagnosis	Disease Duration at First Mycophenolate Mofetil Treatment, y	NMO-IgG Status	LETM on MRI	Drugs Used Prior to Mycophenolate Mofetil	Concomitant Immunotherapy
1/M	Relapsing myelitis	3	+	+		
2/M	NMO	4.08	+	+	Azathioprine	
3/F	NMO	6.83	+	+	Interferons	Oral prednisone
4/F	NMO	5.89	+	+	Azathioprine, interferons, prednisone	
5/F	Relapsing myelitis	0.83	+	+	Azathioprine	Prednisone on alternate days
6/F	NMO	1.17	+	+	Glatiramer acetate	Pulsed intravenous methylprednisone monthly
7/F	NMO	1	U	+		
8/M	Relapsing myelitis	2.75	+	+		
9/F	NMO	12.5	+	+	Azathioprine, prednisone, intravenous immunoglobulins	Intravenous immunoglobulin monthly
10/F	Relapsing myelitis	1.25	+	+		
11/F	Relapsing myelitis	6.25	+	+	Interferon, prednisone	
12/F	Relapsing optic neuritis	10.83	+	-		Oral prednisone
13/F	NMO	26.33	+	+	Azathioprine, interferon, glatiramer acetate, methotrexate	1 g of oral methylprednisone monthly
14/F	NMO	18.16	+	+	Prednisone, glatiramer acetate, mitoxantrone, cyclophosphamide, interferon	
15/F	Single episode of myelitis	0.08	+	+		5 mg of oral prednisone daily
16/F	NMO	13.01	+	+	Azathioprine, intravenous methylprednisone, interferon, mitoxantrone, methotrexate	
17/F	NMO	25.83	+	+	Glatiramer acetate, azathioprine, interferons, prednisone	
18/F	NMO	38.75	+	+	Azathioprine, interferon, intravenous immunoglobulins	
19/F	NMO	0.66	+	+		
20/F	Relapsing myelitis	1.5	+	+	Cyclophosphamide	
21/M	NMO	1.42	+	+	Azathioprine, prednisone	Prednisone, intravenous methylprednisone
22/F	Relapsing myelitis	0.25	+	+	Azathioprine	Pulsed intravenous methylprednisone
23/F	NMO	4.33	+	-	Azathioprine, prednisone, cyclophosphamide	
24/M	NMO	6.5	+	+	Azathioprine, interferon	

Abbreviations: LETM, longitudinally extensive transverse myelitis; MRI, magnetic resonance imaging; NMO, neuromyelitis optica, U, unknown ; +, present; -, absent.

tients were undergoing additional treatments (oral [n=8] and intravenous [n=1] corticosteroids) for variable periods after starting treatment with mycophenolate mofetil (Table).

The median annualized posttreatment relapse rate was 0.09 (range, 0-1.56), and the pretreatment rate was 1.28 (range, 0.23-11.78; $P<.001$, Wilcoxon signed-rank test). Nineteen of the 24 patients (79%) had an improvement in annualized relapse rate. Because analyses of the total group were confounded by short duration of treatment, death, and concomitant treatments, we performed the following 3 subgroup analyses.

Analysis Excluding Patients With Less Than 6 Months of Mycophenolate Mofetil Therapy. Two of the 24 patients took mycophenolate mofetil for a very short duration (patients 1 and 2 for 1 month each) and discontinued taking the drug early owing to adverse effects. With these patients excluded from the analysis, the median treatment duration was 28 months (range, 16-89 months). The median posttreatment annualized relapse rate on treatment for the remaining 22 patients was 0.2 (range, 0-1.5), a significant reduction compared with the pretreatment rate of 1.37 (range, 0.23-11.78; $P<.001$). Seventeen of 22 patients (77%) had an improvement in relapse rate.

Analysis Excluding Those in First Analysis and 1 Patient Death. After exclusion of the patient who died (patient 21) and those excluded in the first subgroup analysis, the median duration of treatment for the 21 patients was 27.4 months (range, 16-89 months). The median posttreat-

ment annualized relapse rate with treatment for this subset was 0.18 (range, 0-1.5), and the pretreatment rate was 1.15 (range, 0.23-11.78; $P<.001$).

Analysis Excluding Those in Second Analysis and Patients Receiving Concomitant Therapies. After exclusion of patients who received concomitant immunosuppressive treatment (patients 3, 5, 6, 9, 12, 13, 15, 21, and 22) and those in the second subgroup analysis, the median duration of treatment in months was 31 (range, 21-89 months) for the remaining 12 patients. The median posttreatment annualized relapse rate on treatment for this subset was 0.24 (range, 0-1.22), and the pretreatment rate was 1.15 (range, 0.23-7.6; $P<.001$).

Disability

The median EDSS score was 6 (range, 0-8) at the start of treatment with mycophenolate mofetil (n=24) and 5.5 (range, 0-10) at last follow-up (at a median of 28 months; $P=.17$). Exclusion of 2 patients who underwent treatment for a very short period did not alter the median scores.

The EDSS scores were unchanged in 15 and improved in 7 (22 of 24 [91%]). The median reduction in EDSS score was 1 point (range, 0-5-2.5). Four of these patients no longer needed a cane. The EDSS score worsened in 2 patients (patient 3 worsened from 6 to 8, and patient 21 died after being bed bound for 54 months).

ADVERSE EVENTS

Patient 21 died. He was a 45-year-old Hispanic man who presented with optic neuritis and myelitis in 1999 and had 3 additional relapses in the same year. He began treatment with mycophenolate mofetil and prednisone in 2000, after developing liver dysfunction with azathioprine. No adverse effects were noted in the first year of treatment. He was subsequently lost to follow-up. Telephone interviews with his family following his death indicate that the patient continued to relapse approximately every 6 months and died 54 months after onset of treatment with mycophenolate mofetil. The death certificate documents the cause of death as "cardiopulmonary failure; respiratory drive failure and Devic's disease."

Six patients (25%) reported adverse effects: headache (n=1), constipation (n=1), easy bruising (n=1), anxiety (n=1), hair loss (n=1), diarrhea and abdominal pain (n=1), and low white blood cell counts that required discontinuation (n=1).

COMMENT

The increasing popularity of mycophenolate mofetil in treating rheumatic disease and myasthenia gravis and in preventing transplant rejection prompted its use for NMO. This retrospective study summarizes the treatment experience at the Mayo Clinic with this drug. Mycophenolate mofetil therapy was associated with an improvement in the relapse rates in 19 of 24 patients (79%) and stabilization or reduction in disability in 22 of 24 patients (91%).

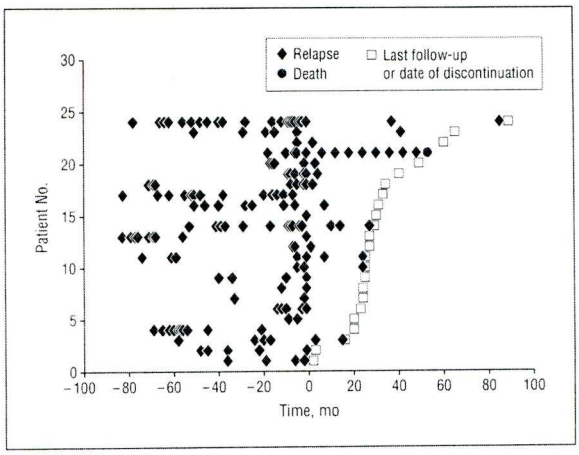

Figure. Neuromyelitis optica relapses before and after treatment with mycophenolate mofetil (0 on the x-axis indicates the start date of treatment). Each interrupted line on the y-axis represents a patient. The relapses of patient 21 are distributed evenly over his mycophenolate mofetil treatment duration owing to incomplete data.

The single previous case report of mycophenolate mofetil in NMO described a 9-year-old girl with NMO who had 5 relapses within a 2-year period despite azathioprine. Corticosteroid therapy was followed by a vertebral fracture. Mycophenolate mofetil introduced 16 months after onset of NMO was followed by sustained remission at 2 years.[17]

The mainstay of treatment for most patients with NMO is prednisone, alone or combined with azathioprine. This approach is largely based on a series of 7 patients with NMO who were treated with long-term prednisone and azathioprine and were followed up every 2 months for at least 18 months. Their EDSS scores improved significantly and no relapses occurred for more than 18 months.[12]

A series of 5 patients treated with mitoxantrone during 2 years also showed improvement.[14] However, 2 patients relapsed once within the initial 5 months of treatment and 1 patient had a reversible decrease in cardiac ejection fraction. Cardiotoxicity is a concern with mitoxantrone, and the duration of treatment is limited to about 2 years because of restricted cumulative lifetime dosing.

Rituximab, a monoclonal antibody against $CD20^+$ B cells,[16] has been used to prevent attacks of NMO. Following up on an initial report on 8 patients, a recent retrospective multicenter experience in 25 patients (23 of whom were refractory to other medications, including 1 patient treated with mycophenolate mofetil) showed that rituximab treatment was associated with reduction in relapse rates and stabilized disability scores in 80% of treated patients.[15,16] However, 28% of patients had infusion-related adverse events and 20% had infections that could have been related, at least in part, to immunosuppression. Two patients died, one likely because of septicemia. Rituximab, therefore, was potentially beneficial but (1) required intravenous infusion (which may necessitate admission), (2) was associated with infection risk, and (3) some patients remained refractory to treatment. These factors and the risks of significant infections from

immunosuppression may limit its use, especially as a first-line agent in the treatment of NMO spectrum disorders.

Mycophenolate mofetil may also produce serious toxicity. Progressive multifocal leukoencephalopathy has been reported in kidney, heart, and lung transplant patients and in systemic lupus erythematosus when mycophenolate mofetil was used in conjunction with or after the use of other immunosuppressants.[28] A retrospective cohort study of 32 757 renal transplant recipients using the United States Renal Data System kidney transplant files identified 9 cases. The incidence of progressive multifocal leukoencephalopathy in those taking mycophenolate mofetil was 14.4 cases per 100 000 person-years at risk vs 0 for those not taking mycophenolate mofetil. However, because 75% of patients in the cohort were taking mycophenolate mofetil, the putative association was not statistically significant. No cases of progressive multifocal leukoencephalopathy were found in patients undergoing mycophenolate mofetil monotherapy.[29] Although an increased risk of lymphoma was initially reported in patients who underwent transplants and occasionally in autoimmune disorders,[30-33] an international prospective registry of 6751 patients receiving mycophenolate mofetil and an equal number of matched controls receiving other immunosuppressive treatments did not find an association with lymphoma in renal transplant patients with lupus nephritis.[34] The adverse effects observed in the present study were dose limiting in 1 patient and necessitated change to azathioprine in another.

The efficacy of mycophenolate mofetil remains uncertain. Despite anecdotal evidence supporting its effectiveness in myasthenia gravis,[19] 2 recent large randomized trials reported no benefit.[35-37] It has not been established whether mycophenolate mofetil is superior to azathioprine in preventing acute rejections in recipients of cadaver kidney transplants.[38] Mycophenolate mofetil is considerably more expensive than azathioprine, but less expensive than rituximab. The estimated drug cost for 1 year of treatment, exclusive of cost of administration, is $846.80 for 150 mg of azathioprine per day, $11 373.40 for 2000 mg of mycophenolate mofetil per day, and $23 287.60 for four 1000-mg infusions of rituximab per year.

The uncontrolled design of the study, the small sample, and confounding concomitant treatments preclude definitive evaluation of the efficacy of mycophenolate mofetil for NMO relapse prevention. The reduction in the posttreatment relapse rate could be explained by regression to the mean.[39] The effects of EDSS score could have been confounded by recent attacks at the time of initiation of mycophenolate mofetil treatment and effects on attack suppression. There was no washout period to eliminate effect of prior therapies. Follow-up was incomplete, and the cause of death in 1 patient had to be ascertained by contact with his family and review of the death certificate.

This is a cumulative experience of all patients with NMO treated by 10 neurologists at 3 different Mayo Clinic sites. Despite the aforementioned limitations, this case series provides some justification for the use of mycophenolate mofetil to prevent attacks of NMO. There have been no placebo- or active comparator–controlled trials in NMO. Azathioprine with or without oral prednisone, rituximab, mycophenolate mofetil, and other immunosuppressants all seem effective; therefore, adverse effects and cost along with the urgency to achieve immediate immunosuppression influence the choice of treatment. Controlled trials are necessary.

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